STATISTICAL ANALYSIS PLAN

Pegcetacoplan
PHASE 3

A Phase 3, Randomized, Multicenter, Open-Label, Controlled Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)

PROTOCOL IDENTIFIER: APL2-308

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Apellis Pharmaceuticals, Inc

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Class
BLQ	Below Limit of Quantification
BMI	Body Mass Index
CBER	Center for Biologics Evaluation and Research
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CRO	Clinical Research Organization
DMC	Data Monitoring Committee
DRC	Data Review Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
Hb	Hemoglobin
ICE	Intercurrent Event
ITT	Intention-To-Treat
IRT	Interactive Response Technology
LLN	Lower Limit of Normal
LASA	Linear Analog Scale Assessment
LDH	lactate dehydrogenase
LOV	Last Observed Value
LVOT	Last Value on Treatment
MAR	Missing at Random
MCMC	Monte Carlo Markov Chain
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model for Repeated Measures
MNAR	Missing not at Random
PCS	Potentially Clinically Significant
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per-Protocol
PRBC	Packed red blood cell
PT	Preferred Term (MedDRA)
QOL	Quality of Life

QLQ-C30	EORTC Quality of Life Questionnaire – Core 30 Scale
QTcB	QT Interval Corrected for Heart Rate Using Bazett's Formula
QTcF	QT Interval Corrected for Heart Rate Using Fridericia's Formula
RBC	Red Blood cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SE	Standard Error
STD	Standard Deviation
SI	Système International
SOC	System Organ Class
SOC	Standard of Care
TA	Transfusion Avoidance
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal
WHO	World Health Organization

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 09 November 2018, incorporating the most recent amendment # 3 (10 Aug 2020). 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

2.1 Objectives

The primary objective of this study is to evaluate the efficacy of pegcetacoplan, compared to SOC (excluding complement inhibitors), in patients with paroxysmal nocturnal hemoglobinuria (PNH).

2.2 Endpoints

2.2.1 Primary Endpoint

- Hemoglobin stabilization defined as avoidance of a > 1 g/dL decrease in Hb levels from Baseline in the absence of transfusion through Week 26 (Yes/No)

  AND

- Reduction in lactate dehydrogenase (LDH) level from Baseline to Week 26

2.2.2 Secondary Endpoints

- Hemoglobin response (Yes/No) in the absence of transfusions (Hb response is defined as a ≥1g/dL increase in Hb from Baseline at Week 26)
- Change from Baseline to Week 26 in absolute reticulocyte count (ARC)
- Change from Baseline to Week 26 in Hb level
- Proportion of subjects who received transfusion or had decrease of Hb > 2 g/dL from Baseline (Yes/No).
- Transfusion avoidance (TA) (Yes/No), defined as the proportion of subjects who do not require a transfusion during the Randomized Controlled Period (RCP).
- Number of packed red blood cell (PRBC) units transfused from Baseline through Week 26
- Change from Baseline to Week 26 in Functional Assessment of Chronic Illness Therapy- (FACIT-Fatigue) Scale score

- Normalization of Hb levels (defined as ≥1xLLN) from Baseline to Week 26 in the absence of transfusions (Yes/No)
- Normalization of LDH levels (defined as ≤1 x ULN) from Week 4 to Week 26 in the absence of transfusions (Yes/No)
- Change from Baseline to Week 26 in European Organization for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire (QLQ-C30) scores (version 3)
- Change from Baseline to Week 26 in Linear Analog Assessment (LASA) scale scores (Version 3)
- Absolute reticulocyte count (ARC) normalization (defined as <1 x ULN) at Week 26 in the absence of transfusion (Yes/No)
- Time to failure of Hb stabilization
- Time to first transfusion

2.2.3 Exploratory Endpoints

- CCI
- [redacted]

2.2.4 Safety Endpoints

- Incidence and severity of treatment-emergent adverse events (TEAEs)
- Incidence of thromboembolic events
- Changes from Baseline in laboratory parameters
- Changes from Baseline in electrocardiogram (ECG) parameters
- Incidence of anti-pegcetacoplan antibodies

2.2.5 Pharmacokinetic Endpoint

Pegcetacoplan pharmacokinetics (PK), as assessed by:

Pegcetacoplan PK concentrations from baseline to Week 26

2.2.6 Pharmacodynamics Endpoint(s)

Pegcetacoplan pharmacodynamic (PD), as assessed by:

- Change from Baseline to Week 26 in PNH clone distribution (red blood cells [RBCs] and white blood cells [WBCs])
- Change from Baseline to Week 26 in complement component 3 (C3) deposition in PNH Type II and III RBCs
- Complement levels from Baseline to Week 26 (e.g., total hemolytic complement activity assay [CH50], alternate complement pathway assay [AH50], and C3)

3. STUDY DESIGN

3.1 General Description

This is a prospective, randomized, multicenter, open-label, controlled study. The study will consist of a screening period of up to 4 weeks, followed by a randomized-controlled period of 26 weeks. A total of approximately 54 subjects with PNH who meet all the inclusion criteria and none of the exclusion criteria will be randomized (2:1 ratio) to receive either pegcetacoplan or to remain on their current SOC (excluding complement inhibitors) only from Visit 2 (Day 1) to Visit 15 (Week 26). All subjects who complete Visit 15 (Week 26) may roll over into a separate open-label, long-term extension study (APL2-307), or will complete the safety follow-up (Visit 16 [Week 28], Visit 17 [Week 30], and Visit 18 [Week 34]).

Due to COVID-19 pandemic, subjects unable to have central laboratory assessments are allowed to have hematologic parameters analyzed by a certified local lab.

Following Visit 2 (Week 0), subjects assigned to the SOC (excluding complement inhibitors) treatment group who have a Hb level measured by the central laboratory or certified local laboratory that is ≥2 g/dL below the Baseline value will be offered the opportunity to receive escape therapy with pegcetacoplan.

Transfusion history collected at the Screening Visit (Visit 1; up to Week -4) is described in Section 12.1.3 of the protocol. During the study treatment period (Visit 2 [Week 0] to Visit 15 [Week 26]), transfusions (received a transfusion of packed red cells (PRBC)) will be administered if subjects have either of the following:

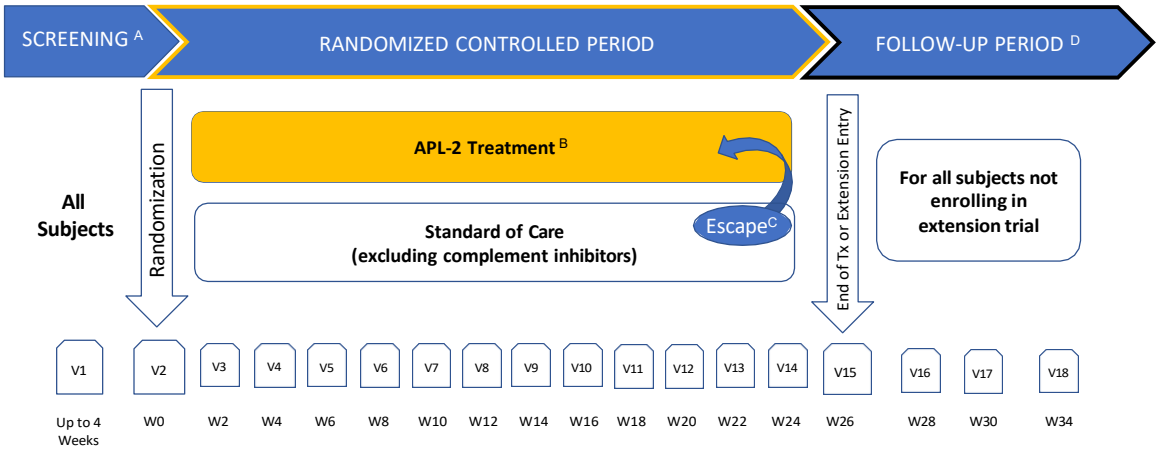
- Hb is <7 g/dL
- Hb ≥7 g/dL - <9 g/dL with symptoms

In addition, Hb, LDH, and Absolute reticulocyte count (ARC) should be collected PRIOR to any transfusion. The assessment may be performed at a central or certified local laboratory.

If these criteria are not met and the PI believes that a transfusion is necessary, the PI should discuss with the sponsor before administering the transfusion. Transfusions that do not meet this criterion will be considered protocol deviations and may lead to data being excluded from the primary analysis.

Figure 1 depicts the study design:

Figure 1APL2-308 study design.



Abbreviations: Tx = treatment; V = visit; W = week.

[a] Screening may occur up to 4 weeks prior to Visit 2. Subjects may proceed from Visit 1 to Visit 2 once eligibility is confirmed (there is no required duration between screening at Visit 1 and Visit 2). Within 5 days prior to Visit 2, each subject's Hb must be evaluated by a certified local or central laboratory. If the subject meets the protocol-specified transfusion guidelines (see Section 10.7 of the protocol), the subject must receive a PRBC transfusion so that the subject's Hb level no longer meets the protocol-specified requirements for PRBC transfusion. The post-transfusion Hb value should be confirmed by a certified local or central laboratory. Subjects must not be randomized if they meet the protocol-specified requirements for transfusion.

[b] Subjects randomized to pegcetacoplan will be assigned pegcetacoplan at a dose of 1,080 mg twice weekly. The dose may be adjusted to pegcetacoplan at a dose of 1,080 mg every 3 days (see Section 10.2.3.2 of the protocol).

[c] Subjects assigned to the SOC (excluding complement inhibitors) treatment group will commence escape pegcetacoplan therapy if they are classified as a failure for the first co-primary endpoint.

[d] All subjects who complete Visit 15 (Week 26) and do not elect to participate in the open-label extension study (APL2-307) will be asked to return to the Investigator site for the Visit 16 (Week 28), Visit 17 (Week 30), and Visit 18 (Week 34) follow-up visits. Subjects who discontinue treatment will be encouraged to continue to attend study visits to complete study assessments (except for treatment with pegcetacoplan), as detailed in the Schedule of Events. At a minimum, subjects who discontinue dosing should complete follow-up procedures outlined in the Schedule of Events 2, 4, and 8 weeks after treatment discontinuation. If withdrawal of pegcetacoplan treatment is necessary, slow weaning should be considered and subjects should carefully be monitored for at least 8 weeks to detect serious hemolysis or other complications, as detailed in the IB.

3.2 Randomization

Subject numbers will be assigned to subjects as they consent to take part in the study.

A total of approximately 54 subjects who meet all the eligibility criteria and none of the exclusion criteria will be randomized (2:1 ratio) to receive either pegcetacoplan or current SOC (excluding complement inhibitors) using interactive response technology (IRT).

Randomization will be stratified by the number of PRBCs transfused within the 12 months prior to screening (<4; ≥4) (i.e., number of transfusion events regardless of PRBC units transfused).

3.3 Sample Size and Power Considerations

A total of 48 randomized subjects (32 subjects to pegcetacoplan and 16 subjects to SOC) are required to achieve 90% power, at the 5% significance level (2-sided), using a 2-group Fisher's exact test with unequal allocation 2:1 to treatment groups (pegcetacoplan and SOC). Calculation assumes an increase of 45% in the proportion of subjects achieving Hb stabilization with pegcetacoplan, compared to SOC (i.e., a change from 5% [no treatment] to 50% [pegcetacoplan]). With the same number of subjects and assuming an effect size of at least 1.2, the study will be at 96% power for the LDH reduction endpoint.

To account for loss of power due to discontinuations, the study will attempt to randomize 54 subjects.

3.4 Preservation of Type I Error

To preserve the Type 1 error, a fixed sequence testing strategy will be used; hence, statistical significance with the first secondary endpoint (Week 26 Hb response in the absence of transfusion [Yes/No]) will only be concluded if statistical significance is achieved with the primary analysis of the co-primary endpoints.

The ordering of the secondary endpoints in this testing strategy will match the order in which they are presented in Secondary Efficacy Endpoints (see section 2.2.2).

3.5 Pre- and During COVID-19 Pandemic

The Pre- and During COVID-19 Pandemic is defined as follows:

- Pre-COVID-19 is any subject who completed the week 26 visit (RCP) before the beginning of the pandemic (March 11, 2020).
- During COVID-19 is any subject who completed the week 26 visit (RCP) during or after the beginning of pandemic (March 11, 2020).

4. STATISTICAL ANALYSIS SETS

4.1 Screened Set

The screened set will include all subjects who provided written informed consent. This set will be used only for the purpose of describing subject disposition.

4.2 Intent-to-Treat Set

The ITT set will include all randomized subjects. Subjects will be analyzed according to their assigned treatment, regardless of the treatment actually received.

4.3 Safety Set

The safety set will include all subjects who receive at least 1 dose of study medication (pegcetacoplan), and subjects who are randomized to SOC (excluding complement inhibitors). Subjects will be analyzed according to the treatment they received.

4.4 Per-protocol Set

The per-protocol (PP) set will include all subjects in the ITT set who did not have any major protocol deviation (PD) that could potentially impact final data analyses (see section 5.7 for detail).

Subjects who have had major protocol deviation, including but not limited to:

a- eligibility violation,

b- taking prohibited medications, and

c- missing 3 or more consecutive study visits, which may impact the interpretation of safety and efficacy will be excluded from Per Protocol analysis.

Decisions concerning the inclusion or exclusion of subjects from the PP analysis set will be made and documented prior to database lock.

4.5 Pharmacokinetic Set

The Pharmacokinetic (PK) set will include all subjects in the ITT analysis set who have at least 1 evaluable (i.e. not impacted by any major protocol deviations or other events) post- dose PK measurement (even if below the limit of quantification). The analyses using this set will be based upon the actual treatment received.

4.6 Pharmacodynamic Set

The Pharmacodynamic (PD) set will include all subjects in the ITT analysis set who have at least 1 evaluable (i.e. not impacted by any major protocol deviations or other events) post-dose PD measurement. The analyses using this set will be based upon the actual treatment received.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

For the Screened set, the number and percentage of subjects screened, who failed screening and the reason for screen failure will be summarized.

For the Safety set, the following will be presented by treatment group and overall:

- Number and percentage of subjects who received at least one dose of randomized treatment (pegcetacoplan or SOC, and total)
- Number and percentage of subjects who completed study treatment.
- Number and percentage of subjects who completed the study pre- and during COVID-19 pandemic.
- Number and percentage of subjects who discontinued study treatmen.t

For those subjects who discontinue study treatment, the reason for discontinuation will be summarized for the Randomized Controlled Period (Visit 2 (Week 0) to Visit 15 (Week 26) (Adverse Events, Withdrawal by Subject, Lost to Follow-Up, Pregnancy, death, Failure to Meet Randomization Criteria, Non-Compliance with Investigation Product, Protocol, Requirements, or Study Related Procedures, Physician Decision, Site Terminated by Sponsor, and Other).

- Number and percentage of subjects who completed the study.
- Number and percentage of subjects who enter the extension study.
- Number and percentage of subjects who withdrew from the study.
- Number and percentage of subjects who discontinue from the study due to COVID-19 pandemic.
- Number and percentage of subjects who Receive a transfusion during the randomized Controlled Period.
- Number of subjects withdraw from study due to receiving transfusion
- Number and percentage of subjects who Withdrew from the study before Week 26.
- Number and percentage of subjects who escape from SOC to pegcetacoplan during the Randomized Controlled Period

The number of subjects in each analysis set will be tabulated by treatment group and overall and by region (Latin America, Europe, and Asia pacific) and will be presented in a listing.

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

5.2 Demographic and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group and overall using the ITT and Safety sets (if sets are different).

Demographic variables to be presented include age (years), age category (<65 years, ≥65 -<75, ≥75 -80, ≥80 years, and ≥80 years), sex, race, ethnicity, region, weight (kg), height (m), 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.

Baseline characteristics to be presented include the following:

- Time since diagnosis of PNH (years) to Visit 2 (Week 0)
- Number of transfusions in the last 12 months prior to Visit 2 (Week 0) (<4; ≥4)
- Number of subjects with zero Vs nonzero transfusions.
- Time since last transfusion to Visit 2 (Week 0)
- Hemoglobin level (value recorded at Visit 2 prior to randomization and dosing with pegcetacoplan or SOC)
- Absolute reticulocyte count (value recorded at Visit 2 prior to randomization and dosing with pegcetacoplan or SOC)
- LDH level (value recorded at Visit 2 prior to randomization and dosing with pegcetacoplan or SOC)
- Haptoglobin level (value recorded at Visit 2 prior to randomization and dosing with pegcetacoplan or SOC)
- Total bilirubin level (value recorded at Visit 2 prior to randomization and dosing with pegcetacoplan or SOC)
- Indirect bilirubin level (value recorded at Visit 2 prior to randomization and dosing with pegcetacoplan or SOC)
- Platelet count (value recorded at Visit 2 prior to randomization and dosing with pegcetacoplan or SOC)
- RBC and granulocyte PNH clone size at baseline
- Total FACIT-fatigue score (nominally recorded on Visit 2 prior to randomization and dosing with pegcetacoplan)
- LASA total score

- EORTC QLQ-C30 Global Health score
- genotyping for Gilbert's Syndrome

Baseline values for subjects randomized to the pegcetacoplan or SOC treatment group will be those measurements taken prior to the start of study treatment which will be the average of measurements prior to randomization to the pegcetacoplan or SOC treatment group for efficacy endpoints, but as the last measurement before the first dose of pegcetacoplan or SOC for other endpoints (see sections 6 and 13.2 for details).

5.3 Medical, Thrombosis and Transfusion History

Medical history will be collected at the Screening Visit (Visit 1; up to Week -4 [Day -28]). Medical history relating to Hb levels and pre-transfusion Hb levels in the past year prior to study enrollment will also be collected.

Thrombosis history will be collected at the Screening Visit (Visit 1; up to Week -4 [Day -28]).

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version available. Summaries will be presented for the Safety set by System Organ Class (SOC) and Preferred Term (PT) with numbers and percentages by treatment group and overall. Each subject will be counted only once in each SOC or SOC/PT summary.

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.

A summary of thrombosis history will also be presented for the safety set with numbers and percentages for each type of thrombosis by treatment group and overall.

A summary of transfusion history will also be presented for the safety set with numbers and percentages for each type of transfusion and the number of units transfused by treatment group and overall.

5.4 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary version available. Medication will be presented by ATC level 2 (therapeutic main group) and ATC level 5 (standardized medication name) with numbers and percentages by treatment group

and overall. 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 ATC level 5 class. In cases of ATC level 2 classes or ATC level 5 classes with equal frequencies, medications will be sorted alphabetically.

Prior medications (including vitamins and herbal preparations), including those discussed in the exclusion criteria (Section 9.2 of the protocol), and procedures (any therapeutic intervention, such as surgery/biopsy or physical therapy) the subject takes or undergoes within 28 days (or 2 years for documentation of vaccination [see Section 11.2.2.2 of the protocol]) prior to the start of screening (Visit 1) until the first dose of study drug will be recorded on the subject's CRF.

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and the end of the follow-up period, inclusive.
Hence, medications started before receiving the first dose of the investigation drug but continuing after will be considered as both prior and concomitant medications. The listing of medications will identify prior and concomitant medications.

5.5 Exposure to Investigational Product

The following parameters will be calculated and presented by treatment group for the Randomized Controlled Period (Visit 2 (Week 0) to Visit 15 (Week 26)) using the safety set:

- Total Dose administered (mg)
- Duration of Treatment (days)
- Number and percentage of subjects received infusions.
    - Number and percentage of subjects with all infusions completed.
    - Number and percentage of subjects with any infusions interrupted.
    - Number and percentage of subjects who did not complete the full dose due to infusion interruption.
    - Number and percentage of subjects received only 1, only 2, etc infusion.
- Total number of infusions

- Number and percentage of infusions completed.
- Number and percentage of infusions interrupted.

Total time on study treatment (Days) calculated as the time in days from first study drug infusion date until the last study drug infusion date for the Randomized Controlled Period (i.e., treatment duration = last study drug infusion in the Randomized Controlled Period – first study drug infusion + 1). The data will be summarized by treatment group.
Number of infusions for each subject will summarized using descriptive statistics.

5.6 Measurements of Treatment Compliance

Percent compliance will be calculated for the Randomized Controlled Period using the safety set for the pegcetacoplan treatment group only.

Percent compliance is calculated as total number of study infusions taken from Visit 2 (Week 2) to end of Randomization Controlled Period (Week 26) divided by the total number of expected infusions to end of Randomization Controlled Period.

The percent compliance formula for pegcetacoplan twice weekly dosing is:

$$\text{Percent compliance} = \frac{\text{total number of infusions received.}}{[\text{(last dose date-first dose date +3.5)} / 7] * 2.0} * 100.0$$

The number and percentage of subjects who had a percentage of drug compliance range by increment of 10% (≥ 80% - 90%, ≥ 90 - ≤100%, >100% - ≤120%) will then be presented in a table by treatment group. Summary statistics will also be presented for for the pegcetacoplan treatment group only.

The number of expected doses for the pegcetacoplan treatment group in the Randomized Controlled Period is between 52 to 61 for pegcetacoplan twice weekly or every 3 days, respectively.

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

5.7 Protocol Deviations

Protocol deviations will be recorded by the site separately from the clinical database. The CRO/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 database lock.

For any criteria for protocol deviations that can be completely implemented by a computer program, the detailed algorithm will be agreed upon. Details of such algorithms will be included in the derived dataset specifications and finalized before database lock.

Confirmed major and minor protocol deviations will be documented in the Protocol Deviation tracker for the study. Major/minor protocol deviations will be summarized by category and site for each treatment group (pegcetacoplan and SOC) and overall, for the Safety set and will be listed.

6. EFFICACY ANALYSES

The efficacy endpoints will primarily be evaluated using the ITT set. All statistical testing will be at the 5% level of significance (2-sided) and all point estimates for the comparison between treatment groups will be accompanied by 2-sided 95% confidence intervals (CIs).

Summary Tables

For continuous data, absolute values and changes from baseline will be summarized by treatment group and visit during the Randomized Control Period.

For categorical data, the number and percentage will be summarized by treatment group and visit within the Randomized Control Period.

For second co-primary efficacy endpoint (LDH) and all continuous secondary endpoints, if a subject escape from SOC to pegcetacoplan during the Randomized Controlled Period, their data collected after the escape will be excluded from the calculation of descriptive statistics. Additional summary statistics tables will include all data collected after transfusion or escape.

If a subject escape from SOC to pegcetacoplan, their values will be summarized under the pegcetacoplan / SOC Escape group.

Summary statistics by randomization strata and by treatment group will be presented at each assessment visit during the 26 Week Randomized Controlled Period for all primary and secondary endpoints.

Hemoglobin (Hb) level will also be categorized as increase from baseline (< 1.0 g/dL, ≥1.0 - < 2.0 g/dL and ≥ 2 g/dL) and the number and percentage of each category will be presented by treatment group.

In case a subject completed the study and agreed to enroll in the long-term safety and efficacy study (APL2-307) but are unable due to COVID-19, this subject with delayed enrollment will continue on the current study treatment until enrolling in the APL2-307 and any data collected (e.g. AE, Lab, VS) will be summarized and presented in tables and Listings.

Plots of Continuous Variables

Mean (± SE) plots and mean (± SE) change from baseline for all continuous primary and secondary efficacy variables will be displayed for the Randomized Controlled Period. The plots will be presented by treatment group.

Listings

Absolute values and changes from baseline will be included in the listings. Flags will also be included to identify values that meet the responder/normalization/stabilization criteria.

6.1 Estimands

The co-primary efficacy endpoints are:

- Hemoglobin stabilization defined as avoidance of a > 1 g/dL decrease in Hb levels from Baseline in the absence of transfusion through Week 26 (Yes/No)

AND

- Reduction in lactate dehydrogenase (LDH) level from Baseline to Week 26

The intercurrent events (ICE) that will be considered are:

1. Transfusions
2. Treatment escape
3. Discontinuation of Study Treatment
4. Withdraw from Study
5. Lost to follow up

Transfusions

For any subject who receives a transfusion (per the transfusion criteria listed in Section 10.7 of the protocol), the first co-primary endpoint will be considered failure to achieve Hb stabilization (Composite Strategy).

Treatment Escape

For any subject who escapes from SOC to pegcetacoplan, the response will be considered failure to achieve Hb stabilization for the first co-primary endpoint (Composite Strategy).

Discontinuation of Study Treatment

If a subject discontinues study treatment, any values collected after discontinuation will continue to be used in analyses (Treatment Policy strategy)

Pandemic-Related ICE due to COVID-19

Pandemic related ICE due to COVID-19 (e.g., discontinuation of study treatment, missing outcomes because of missing evaluation visits) is typically unrelated to study medication or outcome, therefore, the Hypothetical Strategy for dealing with this ICE will be used, as it is aligned with the clinical goal of evaluating outcomes that would have been observed had no COVID-19 pandemic interfered with the treatment regimen.

The following table shows the primary Estimands, the sensitivity and the supportive analyses for the co-primary efficacy endpoints.

Definition	Attributes			
	A: Population	**B: Variable (or endpoint)**	**C: Strategy for addressing intercurrent event (ICE)**	**D: Population-level summary**
1- First Co-Primary Endpoint: The effect of pegcetacoplan compared to SOC on Hemoglobin stabilization after 26 weeks of monotherapy treatment to PNH subjects.	ITT	Week 26 Hemoglobin stabilization	The composite strategy will be followed (i.e., Subject who experienced one of the following events will be considered failure): • Transfusions • Treatment escape • Discontinuation of Study Treatment • Withdrawal from the study • Lost to follow up	The adjusted odd ratio (OR) of achieving Hb stabilization for the pegcetacoplan group versus SOC and associated 95% CI will be presented along with the difference between treatment proportion with associated 95% confidence interval and appropriate p-value using CMH.
	Supportive Analyses			
2-Second Co-Primary Endpoint: Reduction in lactate dehydrogenase	ITT, PP	Week 26 Hemoglobin stabilization	The strategy will be the same as for the first co-primary endpoint shown above.	The adjusted odd ratio (OR) of achieving Hb stabilization for the pegcetacoplan group versus SOC and associated 95% CI and appropriate p-value. Logistic regression with the effects of treatment and stratification factor will be used. In case of nonconvergence exact logistic regression with the effects of treatment and stratification factor will be used to compare the two-treatment group and to estimate the p-value.

(LDH) level from Baseline to Week 26	ITT	Week 26 LDH level change from baseline	Any LDH values before escape from SOC to pegcetacoplan will be used in the analysis and all values after the SOC escape will be set to missing.	Difference between treatment means with 95% confidence interval and appropriate p-value based on ANCOVA adjusting for LDH baseline, treatment, and stratification factor.
	Sensitivity Analyses			
	ITT	Week 26 LDH level change from baseline	The strategy will be the same as for the second co-primary endpoint shown above.	Difference between treatment means with 95% confidence interval and appropriate p-value based on Mixed Model for Repeated Measures (MMRM)
	ITT	Week 26 LDH level change from baseline	Imputation based on the delta-adjusted stress testing method (Tipping Point) using the strategy will be the same as for the second co-primary endpoint shown above.	Difference between treatment means with 95% confidence interval and appropriate p-value based on MMRM
	Supportive Analyses			
	ITT	Week 26 LDH level change from baseline	The strategy will be the same as for the second co-primary endpoint with Last observation carried forward (LOCF) approach for handling missing data using the strategy will be the same as for the second co-primary endpoint shown above.	Difference between treatment means with 95% confidence interval and appropriate p-value based on ANCOVA adjusting for LDH baseline, treatment, and stratification factor.

	ITT	Week 26 LDH level change from baseline	The strategy will be the same as for the second co-primary endpoint with Best observation carried forward (BOCF) approach for handling missing data.	Difference between treatment means with 95% confidence interval and appropriate p-value based on ANCOVA adjusting for LDH baseline, treatment, and stratification factor.
	PP	Week 26 Hb change from baseline	The strategy will be the same as for the second co-primary endpoint.	Difference between treatment means with 95% confidence interval and appropriate p-value based on ANCOVA adjusting for LDH baseline, treatment, and stratification factor.

6.2 Analyses of Primary Efficacy Endpoints

6.2.1 First Co-Primary Efficacy Endpoint

For the first co-primary endpoint (Hb stabilization), the number and percentage of subjects who achieve Hb stabilization using ITT set will be computed and compared between treatment groups using a stratified Cochran-Mantel-Haenszel (CMH) chi-square test. The adjusted odd ratio (OR) of achieving Hb stabilization for the pegcetacoplan group versus SOC with associated 95% CI will be presented along with the difference between treatment proportion with associated 95% confidence interval and appropriate p values.

Subjects who receive a transfusion through Week 26 or escape from SOC to pegcetacoplan treatment group or withdraw from the study or treatment or lost to follow up before providing primary efficacy assessment will be categorized as failing to achieve Hb stabilization.

6.2.2 Second Co-Primary Efficacy Endpoint

The second co-primary efficacy endpoint is the change from baseline in LDH level at Week 26.

If a subject escape from SOC to pegcetacoplan treatment group, the LDH level up to escape will be included in the model. If subject receives transfusion, the pre transfusion LDH level from the certified local laboratory will be used, however, if it is not collected or missing, then the pre transfusion central laboratory LDH value will be used.

The following steps will be taken for the analyses:

1. The post baseline missing LDH values will be imputed using Multiple imputation (MI) method with Markov Chain Mont Carlo (MCMC) methodology using PROC MI of SAS with a total of 1000 imputations and the random seed will be 123876. An appropriate transformation such as a natural Log will be utilized to normalize the data before imputation and using the EXP to unnormalize after the imputation utilizing TRANSFORM LOG function in PROC MI or other transformation as appropriate.
2. The MCMC method in PROC MI will be invoked with multiple chains (CHAIN=MULTIPLE), 200 burn-in iterations (NBITER=200) and a non-informative prior (PRIOR=RIDGE=1) to produce complete data set.
3. The change from baseline (CFB) in LDH level to Week 26 visit will be calculated for each of the 1000 completed data sets generated in step 2.
4. Transformation of CFB might be applied to achieve data normality if deemed appropriate.

5. Each of the 1000 complete data sets from Step 3 will be analyzed using analysis of covariance (ANCOVA) with CFB for LDH level at Week 26 as the response variable and with treatment as fixed effect, adjusted for baseline LDH level and stratification factor using PROC GLM or PROC MIXED of SAS.
6. The results obtained in each 1000 imputed data sets, including the treatment differences and their standard errors, will be combined using Rubin's imputation rules (Rubin, 1987) to produce a pooled estimate of the treatment differences, corresponding 95% confidence interval and a pooled treatment effect P-value using PROC MIANALYZE of SAS.

6.3 Sensitivity Analyses of Co-Primary Efficacy Endpoints

Sensitivity analyses will be performed to evaluate the robustness of the results from the primary analysis methods.

No sensitivity analysis is planned for first co-primary analyses and this section presents only the sensitivity analyses for the second co-primary endpoint.

6.3.1 Second Co-Primary Efficacy Endpoints

Mixed model for repeated measures (MMRM) will be used as the first sensitivity analysis for the second co-primary endpoint (change in LDH from baseline at Week 26) after setting values to missing when subjects escape from SOC to pegcetacoplan.

The between-treatment group comparison for the second co-primary efficacy endpoint will be performed using a mixed effect model for repeated measures (MMRM); (Mallinckrodt CH, 2008); The model will include fixed categorical effects for treatment group, study visit, stratification variables (based on transfusion history) and the study visit-by-treatment group interaction, as well as the continuous, fixed covariate of baseline LDH level. Initially an unstructured covariance matrix will be investigated. If this analysis fails to converge, other structure will be tested such as compound symmetry (CS). The Kenward Roger's approximation will be used to estimate denominator degrees of freedom.

The difference between pegcetacoplan and SOC mean LDH level changes from baseline at Week 26 will be calculated along with its 2-sided 95% CI and associated P-value from the MMRM model.

The Imputation based on the delta-adjusted stress testing (Tipping Point) analysis will be performed for the second co-primary endpoint (mean LDH level change from baseline at Week 26) using MMRM model.

This method can be considered as sensitivity analysis for the second co-primary Missing at Random (MAR) based analyses where deterioration of the future unobserved outcomes constitutes specific types of departure from the MAR assumption towards the Missingness Not At Random (MNAR) assumption.

The Tipping point imputation approach will be based on the delta-adjusted stress testing method, also known as the tipping point analysis (O'Kelly and Ratitch, 2014, Chapter 7). This method assumes that subjects who discontinue from the pegcetacoplan group experience worsening defined by a pre-specified adjustment in the second co-primary endpoint (LDH level). After the initial imputation, a range of shifts will be added to the imputed missing data in both pegcetacoplan and SOC groups.

6.4 Supportive Analyses of Co-Primary Efficacy Endpoints

6.4.1 First Co-Primary Efficacy Endpoints

The first co-primary efficacy endpoint (Hb stabilization) will also be analyzed using logistic regression with the effects of treatment group and stratification factor included in the model using ITT set. The adjusted odd ratio (OR) of achieving Hb stabilization for the pegcetacoplan group versus SOC with associated 95% CI and associate p-value will be estimated from the final model. In case of nonconvergence exact logistic regression with the effects of treatment and stratification factor will be used to compare the two-treatment group and to estimate the p-value

The analyses will be repeated using the PP set (if sets are different from ITT set).

6.4.2 Second Co-Primary Efficacy Endpoints

Per FDA comments (Letter dated Feb 12, 2020), the second co-primary endpoint (LDH) will be analyzed using an analysis of covariance (ANCOVA) model (ITT set) with a last observation carried forward (LOCF) approach for handling missing data. The ANCOVA model will include terms for treatment as fixed effect, adjusted for baseline LDH level and stratification factor using PROC GLM or PROC MIXED.

The second co-primary endpoint (LDH) will be analyzed using an ANCOVA model (ITT set) with a Baseline observation carried forward (BOCF) approach for handling missing

data. The ANCOVA model will include terms for treatment as fixed effect, adjusted for baseline LDH level and stratification factor using PROC GLM or PROC MIXED.

The LOCF and BOCF imputations analyses will be performed after setting all data after escape from SOC to pegcetacoplan to missing.

The PP set supportive analysis will also be provided for the second co-primary endpoint.

The difference between pegcetacoplan and SOC in mean LDH changes from baseline at Week 26 will be calculated along with its 2-sided 95% CI and p-values.

6.5 Analyses of Secondary Efficacy Endpoints

The secondary endpoints will be analyzed using the ITT set. Summary statistics by randomization strata and by treatment group will be presented at each assessment visit during the 26-week Randomized Controlled Period.

The continuous secondary endpoints will be performed whereby all data after escape to pegcetacoplan will be set to missing for:

- Hemoglobin level
- LDH level
- Absolute Reticulocyte count (ARC)
- Hemoglobin level
- Bilirubin level (Indirect & Total)
- Haptoglobin level
- FACIT-Fatigue scale score
- LASA scores
- QLQ-C30 scores

6.5.1 Categorical Secondary Efficacy Endpoints

The number and percentage of subjects meeting the following criteria will be tabulated by treatment group at Week 26 and the superiority test will be used to compare the 2 treatment groups:

- Hemoglobin response (Yes/No) in the absence of transfusions (Hb response is defined as a ≥1g/dL increase in Hb from Baseline at Week 26)
- Proportion of subjects who received transfusion or had decrease of Hb > 2 g/dL from Baseline (Yes/No).

- Transfusion avoidance (TA) (Yes/No), defined as the proportion of subjects who do not require a transfusion during the Randomized Controlled Period.
- Normalization of Hb levels (Yes/No) (defined as ≥1x LLN) from Baseline to Week 26 in the absence of transfusions (Yes/No)
- Normalization of LDH levels (Yes/No) of ≤1 x the upper limit of normal (ULN) from Week 4 to Week 26 in the absence of transfusions (Yes/No)
- Normalization of ARC levels (Yes/No) of <1 x the upper limit of normal (ULN) at Week 26 in the absence of transfusions (Yes/No)

The hemoglobin response, transfusion avoidance (TA), and hemoglobin, LDH and ARC normalization endpoints are binary responses (i.e., Yes / No); each endpoint will be analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factor at randomization. The odds ratio of being a responder (Yes) on each of the endpoints for the pegcetacoplan vs. SOC and associated 95% confidence interval (CI) will be provided. Subjects who received a transfusion or withdraw or escaped from SOC to pegcetacoplan treatment group or withdraw from the study or treatment or lost to follow up without providing efficacy data at Week 26 will be classified as non-responders in these analyses.

For the transfusion avoidance (TA) endpoint, subjects who received a transfusion will be classified as non-responders in this analysis, otherwise the subject will be classified as responder.

For the proportion of subjects who received transfusion or had decrease of Hb > 2 g/dL from Baseline, the subject will be classified as non-responder in this analysis, otherwise the subject will be classified as responder.

The above binary endpoints will be tabulated by treatment group.

6.5.2 Continuous Secondary Efficacy Endpoints

Change from Baseline Endpoints

Superiority will be assessed for the change from baseline to Week 26 for the continuous secondary endpoints:

The absolute values and changes from baseline in ARC, Hb level, indirect and total bilirubin level, haptoglobin level, FACIT-Fatigue scale score. LASA scores and QLQ-C30 scores will be summarized by treatment group at Baseline and each study visit.

The indirect bilirubin is not reported in the database and it will be derived from the total and direct bilirubin as follow:

indirect bilirubin = total bilirubin – direct bilirubin

The Change from baseline at Week 26 will be analyzed using the same methods described for the primary analysis of the second co-primary endpoint, except using their own baseline as a covariate. The ITT set will be used. These analyses will be done by setting values to missing after subject escape to pegcetacoplan from SOC.

Number of PRBC units and Number of Transfusions

The number of PRBC from Baseline to Week 26 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).

The total number of units of PRBCs transfused and number of transfusions during the Randomized Controlled Period will be compared between the treatment groups using Wilcoxon rank-sum test. The difference between the medians will be estimated along with its 95% confidence interval (stratified).

The following supporting analyses for the number of PRBC units and number of transfusions to account for subjects who withdraw during the Randomized Controlled Period before Week 26 will be provided:

- The number of units of PRBCs transfused and the number of transfusions will be analyzed using log-incidence density ratios (non-parametric) adjusting for treatment (Dmitrienko & Koch). For each treatment, the incidence density will be the number units of PRBCs transfused or number of transfusions that a subject experienced, normalized by the number of days during the Randomized Controlled Period.

- The number of units of PRBC and the number of transfusions will be estimated based on the duration they were in the Randomized Controlled Period (i.e.

number per week x duration of endpoint). Hence the analysis of this endpoint will equate to an analysis of the frequency of transfusions.

Time to failure of Hb Stabilization and Time to Transfusions

For the secondary endpoints of Time to first-on-study failure of Hb Stabilization and Time to Transfusions, Kaplan-Meier method will be used to describe the survival data. The comparison of the median survival time between treatment group will be assessed using log-rank test and generalized Wilcoxon test. The subject who lost to follow-up, discontinue the study or escape will be censored at the last visit. For subject who randomized but did not receive any treatment will be censored at the date of randomization. For subject who missed ≥ 3 consecutive visits will be censored at the visit before the first missing visit. For censored subjects, the time to the last observation date will be used for the Kaplan-Meier plot. The hazard ratio (HR) of the pegcetacoplan group to SOC and associated 95% CI will be provided.

The Time to first-on-study escape from SOC to APL-2 group will also be analyzed and presented in table and figure.

6.6 Subgroup Analyses

The co-primary endpoints will be summarized and analyzed by the following subgroups using the ITT set:

1-Number of PRBC transfusions within the 12 months prior to Day -28 (<4; ≥4) (i.e., number of transfusion events regardless of PRBC units transfused.

2- Summary statistics of the co- primary endpoints will also be provided for subgroups based on sex, race, and age (≤65 years and > 65 years).

6.7 Exploratory Endpoints

- CCI
- [redacted]

6.8 Additional Secondary Efficacy Endpoints

The following additional secondary endpoints will also be summarized by treatment group using ITT set:

1. Number and percentage of subjects achieved Hb level ≥ 11 g/dL and ≥ 12 g/dL at week 26.
2. Number and percentage of subjects without PRBC transfusion during the RCP.
3. Total and Indirect Bilirubin normalization levels (defined as <=1xULN) at Week 26 in the absence of transfusion (Yes/No).
4. Number and percentage of subjects achieving ≥ 3 points improvement in FACIT-Fatigue score from baseline to Week 26.
5. Normalization of Hb levels (defined as ≥1xLLN) from Baseline at Week 26 in the absence of transfusions (Yes/No)
6. Normalization of LDH levels ≤1 x the upper limit of normal (ULN) at Week 26 in the absence of transfusions (Yes/No)
7. Absolute reticulocyte count (ARC) normalization (<1 x ULN) from Baseline to Week 26 in the absence of transfusion (Yes/No)
8. Normalization of LDH levels (Yes/No) of ≤1 x the upper limit of normal (ULN) from Baseline to Week 26 in the absence of transfusions (Yes/No)
9. Normalization of Hb levels (defined as ≥1xLLN) from Week 4 to Week 26 in the absence of transfusions (Yes/No)
10. Absolute reticulocyte count (ARC) normalization (<1 x ULN) from Week 4 to Week 26 in the absence of transfusion (Yes/No)

7. SAFETY ANALYSIS

The safety analysis will be performed using the Safety set. For each safety variable, the last value collected before the first dose of investigational product will be used as baseline for all analyses of that safety variable. Last Observed Value on Treatment (LVOT) will be defined as the last valid assessment obtained after Baseline and whilst on investigational product. Last Observed Value (LOV) will be defined as the last valid assessment obtained after Baseline.

All safety data available at the time of database lock for Week 26 will be provided. Safety analyses will be conducted according to the treatment the subject received.

7.1 Adverse Events

Adverse events will be coded using the Version 23.0 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 for APL2 group, on or after randomization date for SOC group or if it has a start date before the date of the first dose but increases in severity on or after the date of the first dose. 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 in summaries. An AE that occurs more than 8 weeks (week 34 or visit 18) after the date of the last dose will not be counted as a TEAE.

Only TEAEs will be included in the summary tables.

An overall summary will be provided for the Randomized Controlled Period of the study as follow:

- any TEAE
- any TEAE considered as related to pegcetacoplan (evaluated by the investigator as definitely related, possibly related)
- any TEAE considered as related to SOC (evaluated by the investigator as definitely related, possibly related)
- any TEAE considered as related to infusion procedure (evaluated by the investigator as definitely related, possibly related)
- maximum severity TEAE of mild, moderate, or severe, i.e. a subject with TEAEs at different intensities will be summarized at the most severe intensity

- any injection site reaction
- any serious TEAE
- any serious TEAE considered related (definitely, probably, possibly) to either study drug.
- any TEAE leading to death.
- Any treatment emergent infections, serious infections, and related infections
- Exposure-Adjusted Incidence TEAE, SAE and ISR.
- TEAE Reported by 5% or More Subjects in Any treatment group.
- Time to Onset of TEAE of Special Search Category
    - Hemolytic Disorders
    - Hypersensitivity
    - Sepsis
    - Infections
    - Thrombosis
- TEAE without Injection Site Reaction
- Injection Site Reaction TEAE

The number and percentage of subjects reporting TEAEs in each treatment group and overall will be tabulated by system organ class (SOC) and preferred term; by system organ class (SOC), preferred term, and maximum severity. TEAEs 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. Any TEAEs with missing severity information will be taken as severe for these summaries and be footnoted and any TEAEs with missing causality information will be taken as related for these summaries and be footnoted.

AE tabulations will also be summarized over the whole study for pegcetacoplan and SOC up to 8 weeks (week 34 or visit 18) beyond the last dose of study medication.

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, TEAEs will be sorted alphabetically.

All TEAEs will be listed by treatment group, subject and AE onset date. Onset time since dose (start date/time – dose date/time) and AE duration (stop date/time – start date/time) will be included in the listing; where applicable imputed data will be used for the calculation of onset time and AE duration, but the original dates/time information will be presented in the listing.

The serious AEs and TEAE due to COVID-19 will be identified in the listing.

If there are any deaths a listing will include the date of death and primary cause of death.

7.1.1 Exploratory Adverse Events Endpoint

CCI

[redacted]

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 by treatment group. The laboratory values will be compared to its 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 case of using certified local laboratory instead of central laboratory due to COVID-19 pandemic, the units and normal ranges might be different and therefore, there might be a need to convert all units to SI units and the method developed by (Stein, 1992, 2001) may be utilized to normalize laboratory data for the purpose of analyses. If, however, the normal ranges for all laboratories are close to each other, global normal ranges may be created for each laboratory parameter to be used for the analyses.

The formula for normalizing the laboratory parameters values is as follow:

$$Z = (X-X_L) / (X_U-X_L),$$

Where Z is the normalized laboratory value,
X is the original laboratory value,
X_U-X_L are the lower and upper normal range values.

Under this rule, values within the normal range transform into those between 0 and 1. The lower bound X_L becomes 0 and the upper bound X_U becomes 1. On the other hand, values outside the normal range transform to either negative values or values above 1. This method is applicable to all lab values without making any distributional assumptions.
Since the normalized values are unit free, we can pool the normalized values from different centers and use them directly in the computation. The original units can be restored, and summary statistics will be present either without units or with the original units.

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

$$Central\ value\ = NRLO(CL) + \frac{local\ value - NRLO}{NRHI - NRLO} \times (NRHI(CL) - NRLO(CL))$$

Were,

NRLO: Low normal range for local lab
NRHIL: High normal range for local lab
NRLO(CL): Low normal range for central lab
NRHI(CL): High normal range for central lab

Clinical laboratory test values are potentially clinically significant (PCS) if they meet either the low or high PCS criteria listed in Table 2. The number and percentage of subjects with post-baseline PCS values will be tabulated by treatment group and overall. 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, site, baseline, and post-baseline values.

Table 2:Criteria for Potentially Clinically Significant Laboratory Tests			
Parameter	**SI Unit**	**Lower Limit**	**Higher Limit**
Hematology			
Hemoglobin	g/dL		
Mild		10	12
Moderate		7	10
Severe		< 7	
Neutrophils Levels	10^9 cell/L		
Mild		1	1.5
Moderate		0.5	1.0
Severe		< 0.5	
Platelets levels	10^9/L		
Mild		100	150
Moderate		50	100
Severe		< 50	

All laboratory data will be listed for 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.

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 study Period, treatment group, visit (day) and scheduled time.

All vital signs data form clinic visit only will be listed for the Safety set. The listing will include change from baseline values.

7.4 Electrocardiogram (ECG)

QT Analyses will be performed by an external vendor (ERT) and the results will be delivered to Apellis in a separate dataset. 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 study Period, treatment group, visit (day) and scheduled time. The mean of the triplicate measurements will be derived prior to summarizing the data. 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.

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

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:

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 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 for Randomized Controlled Period. 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.

7.5 Other Safety Data

Immunogenicity, physical examination, and pregnancy test data will be listed for the Safety set. For Immunogenicity data, the number and percentage of subjects developing antidrug antibodies (ADA) (anti-pegcetacoplan peptide antibodies and anti-PEG

antibodies), treatment-boosted and treatment-emergent responses where applicable, will be summarized and listed by treatment group.

8. PHARMACOKINETIC ANALYSIS

All summaries and analyses of the pharmacokinetic data will be based on the Pharmacokinetic set.

Pegcetacoplan concentrations reported as below the limit of quantification (BLQ) will be taken as zero for linear plots, and equal to the lower limit of quantification (LLOQ) for semi-logarithmic plots. For the computation of descriptive statistics, BLQ will be taken as zero, except for the calculation of the geometric mean where the LLOQ will be used.

The pegcetacoplan concentrations will be evaluated using the PK analysis set. Pegcetacoplan concentrations will be summarized by treatment group at each scheduled time point using descriptive statistics. If a subject discontinues pegcetacoplan dosing, then concentrations from samples collected more than 1 day after the last dose will be excluded from calculations. Follow-up samples will only be included if within 10% of the scheduled time after the last pegcetacoplan dose.

Samples for PK assessment should not be collected for subjects randomized to the SOC (excluding complement inhibitors) treatment group unless they become eligible for and elect to receive pegcetacoplan escape therapy. If a subject from the SOC (excluding complement inhibitors) treatment group is to begin receiving pegcetacoplan escape therapy, a pre-dose PK sample should be collected at the pegcetacoplan initiation visit before dosing begins and at each subsequent visit as detailed in the Schedule of Events. Pegcetacoplan concentrations for the SOC group will be summarized additionally whereby all data after escape is set to missing.

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

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

A listing of all concentration data will be presented by dose. The actual time, deviation and percent deviation from nominal time will also be listed.

Population pharmacokinetic and exposure-response modelling of the safety and efficacy data will be described in the pegcetacoplan Population pharmacokinetic/Pharmacodynamic Analysis Plan which will be performed by consultant or CRO. The methods will be based on the FDA Guidance for both Exposure-Response and Population Pharmacokinetics (FDA Guidance for Industry Population Pharmacokinetics, FDA Guidance for Exposure-Response Relationships).

9. PHARMACODYNAMIC ANALYSIS

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

Observed values, changes from baseline and percentage changes from baseline will be summarized by treatment group at each visit using descriptive statistics for the following parameters:

- Change from Baseline to Week 26 in percentage of PNH Type II+III RBC cells opsonized with C3
- Change from Baseline to Week 26 in percentage of PNH Type II+III RBC cells
- Change from Baseline to Week 26 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).

In addition, the following endpoints will be derived and Changes from baseline and percentage changes from baseline will be summarized by treatment group:

- 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.
- C3d deposition on RBC cells (percent Type II + III); this is the number of events for C3d deposition on RBC cells (Type II) plus number of events for C3d deposition on RBC cells (Type III) divided by number of events for PNH CD59 Type II and III expressed as a percent.

Median profile plots will also be presented graphically by treatment group for the observed values and percentage changes from baseline. The nominal sampling time will be used on the x-axis.

Changes from baseline and percentage changes from baseline will be included in listings.

10. OTHER ANALYSES

No other analyses are planned for this study.

11. INTERIM ANALYSIS

No interim analysis is planned.

12. DATA MONITORING COMMITTEE/REVIEW COMMITTEE

A DMC will review cumulative safety/tolerability data (e.g., physical examinations, ECGs, vital signs, clinical laboratory tests, and AEs), efficacy (Hb and LDH levels, haptoglobin level, ARC, and RBC transfusions), and PK data. The DMC will have the responsibility to conduct a thorough safety assessment at regular pre-defined intervals during the study, as described in the DMC charter.

In addition, an ad hoc data review may be recommended by the DMC or requested by the sponsor at any time during the study.

The DMC charter will be prepared in a separate document.

13. DATA HANDLING CONVENTIONS

13.1 General 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 summaries 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 for the treatment group will be the denominator.

13.2 Definition of Baseline

Unless stated otherwise, baseline will be taken as the average of measurements prior to the first dose of pegcetacoplan or prior to randomization of SOC treatment group for efficacy endpoints, but as the last measurement before the first dose of pegcetacoplan or SOC for other endpoints.

Note: For SOC treatment group, any Lab taken on the randomization date will be included in the baseline calculation.

The average baseline value for Hb, LDH and ARC will include certified local laboratory and central values for those subjects who have transfusions during the screening Period. All other Laboratory parameters, the average baseline values will be from central laboratory values only.

13.3 Summary Table and Listing Presentations

In by-visit summary tables, the baseline will be summarized using all available data, but also for each visit using only the baseline data from subjects with available data at the visit; hence the mean change from baseline will equal the mean visit value – mean baseline value.

Throughout this document 'change from baseline' refers to the actual change from baseline (i.e., visit value – baseline value).

All data will be listed, and data listings will be presented by study Period and treatment group. Data listings will present study days in addition to dates, where study day is derived as (assessment date – randomization date) +1. Therefore, the date of randomization will be identified as Study Day 1.

13.4 Definition of Visit Windows

Data will be summarized and analyzed based on the list of visits specified in table below. The relative day of each assessment [(date of assessment) – (date for randomization +1] will be calculated for post randomization. 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 that 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.

All assessments that occur on > Day 1 will be assigned to the Randomization Controlled Period, whilst any assessment that occurs prior or equal to Day 1 (≤ Day 0) will be assigned to the screening Period. See the table below for details on visit windows:

Part	Study Visit	Target Day	Analysis Window (days)	Interval
Screening	1	0	-28 - ≤ 0	28
RCP				
	2	1	1 - 8	7
	3	15	9 - 22	13
	4	29	23 - 36	13
	5	43	37 – 50	13
	6	57	51 – 64	13
	7	71	65 – 78	13
	8	85	79 – 92	13
	9	99	93 – 106	13
	10	113	107 – 120	13
	11	127	121 – 134	13
	12	141	135 – 148	13
	13	155	149 – 162	13
	14	169	163 – 176	13
	15	183	177 -190	13
F/U	16	197	191 – 203	13
	17	211	204 -217	13
	18	232	218 - 246	28
	19	261	247 - 275	28
	20	290	276 - 304	28
	21	319	305 - 333	28

	22	348	334 – 362	28
	23	377	363 – 391	28
	24	406	392 – 420	28
	25	435	421 - 449	28
	26	463	450 - 477	28
	27	492	478 - 506	28

13.5 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. Subject 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 Answers 5 and 7) are reversed to ensure that the higher score corresponds to a higher quality of life.

Linear Analog Scale Assessment (LASA)

The Linear Analog Scale assessment (LASA) consists of three items asking respondents to rate their perceived level of functioning. Specific domains include activity level, ability to carry out daily activities, and an item for overall QOL. Their level of functioning is reported on a 0-100 scale with 0 representing "As low as could be" and 100 representing "As high as could be". In addition to looking at each domain the combined score (range of 0-300) will be determined.

European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30 Questionnaire)

The EORTC QLQ-C30 questionnaire (version 3.0) consists of 30 questions comprised of both multi-item scales and single-item measures to assess overall quality of life in subjects. Questions are designated by functional scales, symptom scales, and global subject QOL/overall perceived health status.

For the first 28 questions the 4 possible responses are "Not at all' (1), 'A little' (2), 'Quite a bit' (3) and 'Very much' (4). For the remaining 2 questions the response is requested on a 7-point scale from 1 ('Very poor') to 7 ('Excellent').

	Number of Items	Item Range*	Item Numbers
Global Health Status / QoL	2	6	29, 30
Functional Scales			
Physical Functioning	5	3	1 to 5
Role Functioning	2	3	6, 7
Emotional Functioning	4	3	21 to 24
Cognitive Functioning	2	3	20, 25
Social Functioning	2	3	26, 27
Symptom Scales			
Fatigue	3	3	10, 12, 18
Nausea and Vomiting	2	3	14, 15
Pain	2	3	9, 19
Dyspnoea	1	3	8
Insomnia	1	3	11
Appetite Loss	1	3	13
Constipation	1	3	16
Diarrhoea	1	3	17
Financial Difficulties	1	3	28

* the item range is the difference between the possible maximum and the minimum response to the individual items, hence for Questions 1-28 this is 3 and for Questions 29 and 30 this is 6.

Once the raw scores are calculated, a linear transformation will be applied to obtain the particular score as follows:

Functional Scale Scores = {1 – (Raw Score-1)/range} x 100
Symptom Scale Scores = {(Raw score -1)/range} x 100
Global Health Status / QoL Scale score = {(Raw score -1)/range} x 100

Hence for the functional scales and the global health status a higher score indicates a better QoL, whilst for the symptom scale scores this is implied by a lower score.

Consequently, each scale has a range of 0% - 100%. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high level of functioning but a high score for a symptom scale represents a high level of symptomatology.

Missing data: in the case of multi-item scales missing one of the items, raw scores can still be calculated using the completed items as long as more than 50% of the items were answered. For single-item measures, the score will be set to missing.

13.6 Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated assessments before the start of investigational product, then the results from the average final assessments made prior to the start of investigational product will be used as baseline. If end of study assessments is 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.

13.7 Handling of Missing, Unused, and Spurious Data

13.7.1 Missing Data Imputation for Efficacy Endpoints

Imputation methods are described in the sensitivity analyses in Section 6.2.2 and appendix 17.3.

13.7.2 Missing Date of Investigational Product

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

For prior or concomitant medications, including the rescue medication of SOC, incomplete (i.e., partially missing) start date and/or stop date will be imputed.

For a missing start date (where stop date is after start date of pegcetacoplan dosing or missing) the date will be imputed as the first dose date of pegcetacoplan; for a missing stop date the date will be imputed as the last study date.

The original dates (as recorded in the eCRF) will be presented in listings.

13.7.2.1 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.

13.7.2.1.1 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.

13.7.2.1.2 Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure in section 13.7.2.1.1.

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

13.7.2.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of 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. If both start date and stop date are missing, then there will be no imputation.

13.7.2.2.1 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 the last day and month of the year (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 the first day and month of the year (01 January) will be assigned to the missing fields.

13.7.2.2.2 Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the procedure for Missing Day and Month.

13.7.2.2.3 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 date of the last dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the last dose of 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.

13.7.3 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, and the calculation of study onset day, study stop day and duration. 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.

For a missing start date (where stop date is after start date of pegcetacoplan dosing or missing) the date will be imputed as the first dose date of pegcetacoplan; for a missing stop date the date will be imputed as the last study date.

The original dates (as recorded in the eCRF) will be presented in listings.

13.7.3.1 Incomplete Start Date

Follow the same rules as in Section 13.7.2.1.2.

13.7.3.2 Incomplete Stop Date

Follow the same rules as in Section 13.7.2.2.

13.7.4 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.

13.7.5 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 double-blind investigational product will be used for incidence summaries, while both the actual and the imputed values will be presented in data listings.

13.7.6 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.

14. ANALYSIS SOFTWARE

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

15. CHANGES TO ANALYSES

15.1 Changes to Analyses Specified in the protocol

The following changes have been introduced in this version of the SAP from the most recent protocol:

- The second co-primary analysis specified in the protocol has been replaced by an ANCOVA analysis. The analysis specified in the protocol (MMRM) is performed as a sensitivity analysis.
- Three Sensitivity analyses for the second co-primary endpoints (change from baseline to Week 26 for LDH) were added; 1) MMRM, 2) control-based imputation method and 3) tipping point analysis based on the delta-adjusted stress testing method. These analyses were not specified in the protocol.

15.2 Changes from Analyses Specified in the Previous Version of the SAP

- The criteria of setting to missing continuous efficacy parameters were changed to: "values after SOC escape to pegcetacoplan will be set to missing" from

  "Any continuous values before escape from SOC to pegcetacoplan will be used in the analysis and all values after the SOC escape or have transfusion or discontinue the study or lost to follow up will be set to missing)" due to medical reasons.
- On page 50, under section 13.7.2.1.2, 13.8.2.1.1. was changed to 13.7.2.1.1.
- Added additional analysis visit windows to cover subjects' visits waiting to enroll in the LTSE (APl2-307) study.
- Removed All available data analyses as it is no longer applicable for continuous variable analyses.
- Removed by COVID-19 analyses as we have only 2 subjects completed the study before March 11, 2020.
- Removed "controlled-based imputation" analyses for the second co-primary endpoint.
- Removed Completer set.
- CCI
- The Logarithmic transformation was added to the multiple imputations to normalize the data as the MCMC assumes multivariate normal and LDH data is skewed to the right which gives unreasonable output after imputations if not normalized.

15.3 Changes from Analyses Specified in Version 2.0 of the SAP

The following changes were made to address numerical issues with statistical modeling and maintain consistency in the analysis of laboratory-based secondary endpoints prior to data cut date (April 29, 2021).

- Logistics regression is a supportive analysis for the first co-primary endpoint (Hb stabilization). Because the responder rate may be rare for the SOC group, the logistic regression model may not converge. In case of non-convergence, an exact logistics regression will be used instead to compare the treatment groups.
- Due to small sample size and a high rate of missing data subsequent to intercurrent events for the SOC group, the multiple imputation procedure with MCMC may have unstable parameter estimation, leading to issues such as non-convergence and extreme samples (i.e., imputed values). Therefore, a ridge prior with one degree freedom (i.e., Ridge=1) will be used in PROC MI procedure to stabilize the parameter estimation, where the small value of 1 is not expected to introduce any bias to the analysis results.
- Added additional secondary endpoint: Normalization of LDH levels (Yes/No) of ≤1 x the upper limit of normal (ULN) from Baseline to Week 26 in the absence of transfusions (Yes/No).
- Normalization of Hb levels (defined as ≥1xLLN) from Week 4 to Week 26 in the absence of transfusions (Yes/No)
- Absolute reticulocyte count (ARC) normalization (<1 x ULN) from Week 4 to Week 26 in the absence of transfusion (Yes/No)
- Treatment compliance was corrected by replacing the 2.5 in the denominator with 2.0.
- Added additional age categories.

16. REFERENCES

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17. APPENDICES

17.1 Schedule of Assessments

Study Period	Screening[A]	Randomized Controlled Period														Follow Up[B]			AIV[C]
Study Week	Up to -4	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	34	--
Study Day	Up to -28	1	15	29	43	57	71	85	99	113	127	141	155	169	183	197	211	239	--
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	--
Clinic Visit Window (±Days)	N/A	0	3	3	3	3	3	3	3	3	3	3	3	3	3	3	7	7	--
Informed Consent	X																		
Demographics	X																		
Height/Weight	X																		
Medical	X																		
Thrombosis history	X																		
Transfusion history	X																		

Study Period	Screen-ing[A]	Randomized Controlled Period														Follow Up[B]			AIV[C]
Study Week	Up to -4	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	34	--
Study Day	Up to -28	1	15	29	43	57	71	85	99	113	127	141	155	169	183	197	211	239	--
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	--
Clinic Visit Window (±Days)	N/A	0	3	3	3	3	3	3	3	3	3	3	3	3	3	3	7	7	--
Inclusion/Exclusion	X																		
Confirm Hb entry criteria[D]		X																	
Randomization		X																	
[redacted]	[redacted]	[redacted]													[redacted]				
Vaccination			X[E]	E			X[E]	E											
Preventive antibiotics[F]		X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
Physical examination[G]	X	X								X					X	X	X	X	
12-lead electrocardiogram[H]	X	X		X		X		X		X		X			X	X	X	X	

Study Period	Screen-ing[A]	Randomized Controlled Period														Follow Up[B]			AIV[C]
Study Week	Up to -4	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	34	--
Study Day	Up to -28	1	15	29	43	57	71	85	99	113	127	141	155	169	183	197	211	239	--
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	--
Clinic Visit Window (±Days)	N/A	0	3	3	3	3	3	3	3	3	3	3	3	3	3	3	7	7	--
PEGCETACOPLAN administration training[I]		X	I																X
PEGCETACOPLAN administration[I]		X																	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital sign measurements[J]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X		X		X	X	X		X	X		X	X	X	X	X	X	
Blood[K]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetics[L]		X		X		X		X				X			X		X		

Study Period	Screen-ing[A]	Randomized Controlled Period														Follow Up[B]			AIV[C]
Study Week	**Up to -4**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**34**	**--**
Study Day	**Up to -28**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**183**	**197**	**211**	**239**	**--**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**--**
Clinic Visit Window (±Days)	**N/A**	**0**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**7**	**7**	**--**
Anti-PEGCETACOPLAN Ab assay		X		X				X			X				X		X		
Direct Antibody Test (Coombs)	X	X		X		X	X	X			X		X	X	X	X	X	X	
Lactate dehydrogenase	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology and chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Absolute reticulocyte count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Haptoglobin	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation profile[M]		X		X		X			X			X			X	X	X	X	

Study Period	Screen-ing[A]	Randomized Controlled Period														Follow Up[B]			AIV[C]
Study Week	**Up to -4**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**34**	**--**
Study Day	**Up to -28**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**183**	**197**	**211**	**239**	**--**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**--**
Clinic Visit Window (±Days)	**N/A**	**0**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**7**	**7**	**--**
Complement profile (CH50, and AH50)		X		X		X		X				X			X		X		
C3 Profile		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Flow cytometry	X	X		X		X				X					X	X	X	X	
Plasma (free) Hb	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Ferritin	X	X		X		X	X	X			X		X	X	X	X	X	X	
Pregnancy (B-HCG) or FSH[N]	X																		
Genotyping for Gilbert's Syndrome[O]	X																		

Study Period	Screen-ing[A]	Randomized Controlled Period														Follow Up[B]			AIV[C]
Study Week	Up to -4	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	34	--
Study Day	Up to -28	1	15	29	43	57	71	85	99	113	127	141	155	169	183	197	211	239	--
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	--
Clinic Visit Window (±Days)	N/A	0	3	3	3	3	3	3	3	3	3	3	3	3	3	3	7	7	--
Urine pregnancy test[P]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
FACIT-Fatigue Scale		X		X		X		X		X		X			X	X	X	X	
LASA Scale		X		X		X		X		X		X			X	X	X	X	

FOOTNOTES:

A. Abbreviations: Ab = antibodies; AE = adverse event; AH50 = alternate complement pathway assay; AIV = pegcetacoplan Initiation Visit; B-HCG = beta-human chorionic gonadotropin; C3 = complement component 3; CH50 = total hemolytic complement activity assay; CRFs = case report forms; ECG = electrocardiogram; eCRF = electronic case report form; EORTC-QLQ-C30 = 30-item European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FACIT = Functional Assessment of Chronic Illness Therapy; FSH = follicle stimulating hormone; Hb = hemoglobin; LASA = Linear Analog Assessment Scale; N/A = not applicable; PCV13 = pneumococcal conjugate vaccine (13-valent); PI = Principal Investigator; PK = pharmacokinetic(s); PPSV23 = pneumococcal polysaccharide vaccine (23-valent); PRBC = packed red blood cell; QTc = corrected QT interval; QTcF = Fridericia's corrected QT interval; SC subcutaneous; SOC = standard of care; WOCBP = women of child-bearing potential.

A Within 5 days prior to Visit 2 (Week 0), each subject's Hb must be evaluated by a local or central laboratory. If the subject meets the protocol-specified transfusion criteria, the subject must receive a PRBC transfusion so that the subject's Hb levels no longer meets the protocol-specified requirements for PRBC transfusion. The post-transfusion Hb value should be confirmed by a local or central laboratory. Patients must not be randomized if they meet

the protocol-specified requirements for transfusion, and the Hb assessment to confirm eligibility should be scheduled so that the subject does not fall outside the screening window (up to Day -28). All Hb levels must be recorded in the eCRF.

B All subjects who complete Visit 15 (Week 26) and do not elect to participate in the open-label extension study will be asked to return to the Investigator site for the Visit 16 (Week 28), Visit 17 (Week 30), and Visit 18 (Week 34) follow-up visits. Subjects who discontinue treatment will be encouraged to continue to attend study visits to complete study assessments (except for treatment with pegcetacoplan) as detailed in the Schedule of Events. At minimum, subjects who discontinue dosing should complete follow-up procedures outlined in the Schedule of Events 2, 4, and 8 weeks after treatment discontinuation. If withdrawal of PEGCETACOPLAN treatment is necessary, slow weaning should be considered and subjects should carefully be monitored for at least 8 weeks to detect serious hemolysis or other complications, as detailed in the Investigator's Brochure.

C Following Visit 2 (Week 0), subjects assigned to the SOC (excluding complement inhibitors) treatment arm who have a Hb level measured by the central laboratory that is ≥2 g/dL below the Baseline value will be switched to escape therapy with pegcetacoplan. These subjects will return to the site for an PEGCETACOPLAN initiation visit. Following the PEGCETACOPLAN initiation visit, subjects will maintain their regular visit schedule.

D The ≤5 day pre-Visit 2 Hb qualification assessment must be assessed to confirm subject eligibility at Visit 2 before the subject can be randomized into the study.

E In order to receive treatment with PEGCETACOPLAN, subjects must have documented evidence of vaccination against the following within 2 years of screening: *Neisseria meningitides* 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).

Subjects randomized to PEGCETACOPLAN: For subjects randomized to pegcetacoplan who do not have documented evidence of receiving any of the above vaccinations within 2 years prior to screening, the required missing vaccination(s) will be administered at Visit 3 (Week 2), prior to dosing with PEGCETACOPLAN (along with boosters administered during the study at or after Visit 7 [Week 10], if required [see below]). Vaccination is mandatory, unless documented evidence exists that subjects are non-responders to vaccination (as evidenced by titers or display titer levels within acceptable local limits). The PI will discuss with the Sponsor regarding individual patient circumstances.

If the subject requires vaccination against *Neisseria meningitidis*, a booster (for both vaccinations) should be administered after at least 8 weeks (Visit 7). If the subject requires vaccination against *Streptococcus pneumoniae*, PCV13 will be administered at Visit 3, and PPSV23 will be administered after at least 8 weeks (Visit 7).

Subjects randomized to SOC (excluding complement inhibitors): Subjects who are initially randomized to SOC (excluding complement inhibitors) who become eligible for pegcetacoplan escape therapy will receive any required vaccination(s) 2 weeks after initiation of treatment with PEGCETACOPLAN. If required, as detailed above), the *Neisseria meningitidis* booster (for both vaccinations), and/or PPSV23 vaccination should be administered at least 8 weeks following the initial vaccination(s).

F In order to receive treatment with PEGCETACOPLAN, subjects will require preventive antibiotics if they need to be vaccinated, as detailed in Footnote E above. In addition, subjects who do not require vaccination are recommended to receive preventive antibiotic therapy, as detailed below.

Subjects randomized to PEGCETACOPLAN: Subjects will be required to take ciprofloxacin 500 mg twice daily from Visit 2 (Day 1) to Visit 3 (Week 2) and continue to receive antibiotic prophylaxis until at least 14 days post vaccination. From that point forward, it is recommended that all subjects take penicillin V 500 mg twice daily through the course of pegcetacoplan treatment.

Subjects randomized to SOC (excluding complement inhibitors): Subjects who are initially randomized to SOC (excluding complement inhibitors) do not need to initiate preventive antibiotic therapy at Day 1. If a subject becomes eligible for and initiates pegcetacoplan escape therapy, the subject should take ciprofloxacin 500 mg twice daily for 2 weeks, beginning on the first day of treatment with pegcetacoplan and continue to receive antibiotic prophylaxis until at least 14 days post vaccination. After 2 weeks of ciprofloxacin, it is recommended that subjects take penicillin V 500 mg twice daily through the course of PEGCETACOPLAN treatment.

G A full physical examination should be conducted, as indicated by the study schedule. A symptom-driven physical examination may be performed at other visits, at the PI's discretion.

H Triplicate 12-lead ECGs are to be performed within 1 hour pre-dose at Visit 2 (Day 1). Triplicate 12-lead ECGs will be performed prior to dosing at all other visits, if PEGCETACOPLAN administration is occurring at the study site. During the study, if the QTcF at any on-treatment ECG is ≥500 ms (mean of QTcF replicate values), the Investigator should perform 3 additional ECGs over 20-60 minutes; if the mean QTcF of the 3 repeat ECGs is ≥500 ms, the site should instruct the subject to return the following day to perform repeat triplicate ECGs. An evaluation will be performed to look for other factors which may have contributed to QTc prolongation (eg, new concomitant medications, hypokalemia, etc.).

I **Subjects randomized to PEGCETACOPLAN:** For subjects randomized to the pegcetacoplan treatment arm, research nurses or other appropriately qualified research personnel will administer the first PEGCETACOPLAN SC infusion at Visit 2 (Day 1) and will train subjects on how to self-administer. Following Visit 2, appropriately qualified research personnel will supervise self-administration of PEGCETACOPLAN for at least the following 3 doses (which will be administered prior to Visit 3). Supervision of self-administration may be conducted at the subject's home, at the study site, or at an off-site location convenient for the subject. Supervision of self-administration must continue until the subject is qualified to self-administer.

Following self-administration qualification, subjects may self-administer pegcetacoplan SC infusions without supervision. Subjects may continue to self-administer infusions at the study site on those days when a study visit occurs, but this is not required. Self-administration conducted at the study site will be supervised to ensure that the subject continues to remain compliant with the administration guidelines. On all other days, subjects may self-administer at home, at the study site, or at an off-site location convenient to the subject.

Subjects randomized to SOC (excluding complement inhibitors): Subjects randomized to the SOC (excluding complement inhibitor) treatment arm that are assigned to PEGCETACOPLAN escape therapy during the study will have research nurses or other appropriately qualified research personnel administer the first PEGCETACOPLAN SC infusion and provide self-administration training at the study visit in which pegcetacoplan escape therapy is initiated. Following this visit, appropriately qualified research personnel will supervise self-administration of pegcetacoplan for at least the following 3 doses at the subject's home, the study site, or an off-site location convenient for the subject. Supervision of self-administration must continue until the

subject is qualified to self-administer, and PEGCETACOPLAN will be self-administered and supervised at the study site on days of study visits, if the subject elects to administer PEGCETACOPLAN during the study visit.

J Vital signs will be measured before venipuncture and ECG. Monitoring of vital signs will occur at Visit 2 (Day 1) pre-dose and 2 hours post-dose (±30 minutes). In addition, monitoring of vital signs will occur pre-dose and 2 hours post-dose (±30 minutes) during the pegcetacoplan Initiation Visit, if applicable. At all other visits, if the subject elects to administer PEGCETACOPLAN during the visit, vital signs should be measured pre-dose.

K If PEGCETACOPLAN will be administered at the study visit, blood samples must be taken pre-dose. The date and time of the last dose of PEGCETACOPLAN should be recorded on the eCRF, as well as the date and time of the blood sample draw (to be used for PK analysis).

L Samples for PK assessment should not be collected for subjects randomized to the SOC (excluding complement inhibitors) treatment arm unless they become eligible for and elect to receive PEGCETACOPLAN escape therapy. If a subject from the SOC (excluding complement inhibitors) treatment arm is to begin receiving PEGCETACOPLAN escape therapy, a pre-dose PK sample should be collected at the pegcetacoplan initiation visit and at each subsequent visit, as detailed in the Schedule of Events.

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

N B-HCG for WOCBP; FSH for post-menopausal women.

O Sample for genotyping to be obtained via buccal swab test completed at the Screening Visit.

P Urine pregnancy test should be completed for WOCBP prior to dosing on Day 1.

Q On the days of clinic visits, an assessment of the PEGCETACOPLAN infusion site will be made as a part of the AE assessment. If PEGCETACOPLAN is administered at the visit, the site staff will observe the dosing and pump-use safety will be assessed and the infusion site will be checked again within 30 minutes after study drug administration. The infusion site assessments will be performed by an appropriately trained staff, as delegated by the Investigator. The infusion site and surrounding area will be inspected for redness, swelling, induration, and bruising. The subject will be asked about the presence of pain and/or tenderness, and any issue related to pump use. The date, time, and outcome of the infusion-site assessment will be recorded on the source documents and CRFs. Subjects will be instructed to notify the PI or other study personnel in the event that an infusion site reaction occurs after self-administration of APL 2. All clinically relevant AEs, as determined by the Investigator, from infusion site or related to pump use will be recorded as AEs.

R Subjects randomized to pegcetacoplan treatment arm or receiving pegcetacoplan escape therapy only.

17.2 Sample SAS codes

17.2.1 Sample SAS Code for First Co-primary and Categorical Secondary Endpoints Analyses

For the first co-primary endpoint (Hb stabilization), the number and percentage of subjects who achieve Hb stabilization (Y/N), the basic SAS code for stratified CMH and CI is shown below:

```
Proc freq data=ADTF;
   tables stragrp1n* arm * avalc  / cmh  riskdiff (common cl= (mn)) ;
  output out=cmh_  cmh;
run;
```

Where;

ADTF is the ADaM efficacy data set

arm is the Randomized treatment group

avalc is the response variable (Y/N) for Hb stabilization

stragrp1n is the stratification variable for randomization

17.2.2 Sample Pseudo SAS Code for Second Co-Primary and Continuous Secondary Endpoints Analyses

For the second co-primary endpoint (change of LDH from baseline to Week 26), the SAS code for imputation is shown below:

```
/* Step 1: Transpose the original data so that there is response at each visit */
/* step 2: Impute all post- baseline missing values for LDH*/

proc mi data = Transpose_Adeff out = LDH_complete  nimpute = 1000 seed = 123876
noprint;
 var  BL STRAGR1N  Wk1 AVAL;
 MCMC IMPUTE = FULL CHAIN= MULTIPLE NBITER=200 PRIOR=JEFFREYS;
 where (arm in ('SOC', 'PEGCETACOPLAN') and paramcd in ('LDH'));
Run;

proc sort data= LDH_complete;
  by _Imputation;
Run;

/* step 3: Compute the change from baseline (CFB) at week 26*/
Data LDH_complete; set LDH_complete;
Where (avisit in ("base, Week 26"));
   Chg = AVAL-Base;
   by _Imputation_;
Run;

/* Step 4: Run ANCOVA at Week 26 only model using proc GLM or MIXED*/

  Proc GLM data = LDH_together_2;
   Class arm stragrp1n;
   Model Chg = base arm StraGrp1N / solution;
   Lsmeans arm / stderr pdiffer cov out=adjmeans;
   ods output lsmeans = lsmeans_ds;
   ds output diffs = diff;
   ods output Tests3 = fixeff;
   by _Imputation_;
```

```
Run;

/* Step 5: Run proc mianalyze at Week 26 with the model effects and standard error */

proc mianalyze data=diff;
modeleffects Estimate;
 stderr StdErr;
 ods output parameterestimates=miparm;
Run;
```

17.2.3 Sample SAS Code for Sensitivity Analyses of Second Co-Primary Endpoint

1- The SAS code for the first sensitivity analyses for the second co-primary endpoint (change from baseline to Week 26 for LDH) using PROC MIXED with MMRM model.

```
Proc mixed data=ADEFF method=reml;

      Class arm avisit(ref="Week 2") usubjid  STRAGR1N;
      Model chg = arm | avisit base STRAGR1N  /  ddfm = kr solution
OUTPM=out_hbModel covb;
      Repeated avisit / type=un subject=usubjid ;
     Lsmeans  arm*avisit / cl  pdiff;
           ods output SolutionF=mxparms CovB=mxcovb;
           ods output lsmeans = lsmeans_ds;
           Ods output diffs = diff;
     ods output Tests3 = fixeff;

Run;
```

Where;

ADEFF is the ADaM efficacy data set

arm is the Randomized treatment group

Resp is the response variable (Y/N) for Hb stabilization

StraGrp1N is the stratification variable for randomization

Chg is the change from baseline for all visit

2- The SAS pseudo code for the second and the third sensitivity analyses for the second co-primary controlled based and Tipping Imputations using PROC MI, MIXED, and MIANALYZE with MMRM model.

The SAS code for imputation of LDH level is shown below:

```
/* Non-Monotone Missing */

/* Step 1: Transpose the original data so that there is response at each visit */

/*Step 2: monotonize both arms separately */
        /*PEGCETACOPLAN   */

proc mi data = ADEFF out = LDH_NMont nimpute = 500 seed = 123876 noprint;
 var base STRAGR1N AVAL;
 MCMC IMPUTE = monotone NBITER=200 PRIOR=JEFFREYS;;
 where (arm in ('PEGCETACOPLAN') and paramcd in ('LDH'));

run;

        /*SOC */

proc mi data = ADEFF out = LDH_complete_SOC nimpute = 500 seed = 123876
noprint;
 var  base STRAGR1N  AVAL;
 MCMC IMPUTE = monotone NBITER=200 PRIOR=JEFFREYS;
 where (arm in ('SOC') and paramcd in ('LDH'));

run;


/* Step 3 Part A */
/* monotone regression pattern for missing data, only need 1 impuation to impose the
monotone reg model */
proc mi data = LDH_complete_SOC out = LDH_Reg_SOC nimpute = 1 seed = 123876
noprint;
 by _Imputation_;
 var  base STRAGR1N AVAL ;
 monotone REG(AVAL = base STRAGR1N);

run;


        /* merge the non-monotone and monotone imputations together */
data LDH_together;
 set LDH_NMont LDH_Reg_SOC;
run;

proc sort data = LDH_together;
 by _Imputation_;
```

```
run;

/* Step 3B: This PROC MI step is only required for Tipping point imputation */
proc MI data = LDH_together out = HB_together_2 nimpute = 1 seed = 123876 noprint;
 by _Imputation_;
 var  base STRAGR1N AVAL ;
 monotone REG(chg = base STRAGR1N);
 mnar adjust(AVAL / shift = &sj);      *←- set sj=0 for controlled based, else Tip value;
run;
/* end for Tipping point imputation */


        /* sort by imputation to fit the proc mixed */
proc sort data = LDH_together_2;
 by _Imputation_ arm STRAGR1N avisit;
run;

        /* Step 4: compute change from baseline for all visits */
 Data LDH_together_2; set LDH_together_2
 Chg= Base – Aval;
Run;

        /* Step 5: the proc mixed step with unstructured covariance structure */


Proc mixed data=HB_together_2 method=reml;
   Class avisit(ref="Week 2") arm subjid STRAGR1N;
    Model chg=arm base STRAGR1N avisit arm*avisit /  ddfm = kr solution
OUTPM=out_hbModel covb;
   by _Imputation_;
   Repeated avisit / type=un subject=subjid ;
    Lsmeans  arm*avisit / cl  pdiff;
   ods output SolutionF=mxparms CovB=mxcovb;
   ods output lsmeans = lsmeans_ds;
   ods output diffs = diff;
   ods output Tests3 = fixeff;
 Run;

        /*Lsmeans diff synthesize the MI from lsmeans diff at each visit*/

proc sort data = diff;
  by _Imputation_ effect;
Run;
```

```
        /*subsets only where you are comparing PEGCETACOPLAN versus SOC at the
same visit */
        /* when the two visits you are comparing are the same you are automatically
        /* comparing PEGCETACOPLAN to SOC */
        /* so you have subset PEGCETACOPLAN versus SOC at Week 2, 4, 8, 12, …,
26, etc */

data diff2;
  set diff;
  where (avisit=_avisit);
run;

proc sort data= diff2;
  by avisit _imputation_;
run;


/* Step 6: proc MIANALYZE at each visit with the model effects and standard error */

proc mianalyze data=diff2;
  by avisit ;
  modeleffects Estimate;
  stderr StdErr;
  ods output parameterestimates=miparm;
 run;

proc print data = miparm;
run;
```

17.2.4 Sample SAS Code for Time to Event Endpoints

For the secondary endpoints of Ttime to failure of Hb Stabilization and Time to Transfusions, Kaplan-Meier method will be used to describe the survival data as shown below:

```
proc lifetest data=ADTTE  plots=(survival (atrisk));
  time TTE*Censored(0);
 strata arm / test=logrank;
run;
```

Where;

ADTTE is the ADaM time to event efficacy data set

arm is the Randomized treatment group

Censored is binary flag to identify the censored observations

17.2.5 SAS Macros for Nonparametric Randomization-Based Analysis using Log-Incidence Density Ratios

%NParCov4(OUTCOMES=count, EXPOSURE= days, HYPOTH=NULL, TRTGRPS=trt, TRANSFORM=INCIDENS, EXACT=YES, NREPS=5000, SEED= 77, DSNIN=indata);

Count is the count of the variable,

Days is the number of days in trial,

Trt is the Randomized treatment group,

Incidens is the number of incidences,

Indata is the name of the data set containing analysis data.

The variance under the null (HYPOTH=NULL) will be used for computing p-values, while the variance under the alternative (HYPOTH=ALT) will be used for computing confidence intervals.

17.3 Sensitivity Analyses for the Primary Efficacy Endpoint

17.3.1 Imputation for the Second Co-primary Efficacy Endpoint

1- Control-based Imputation method

A control-based multiple imputation approach will be used as a sensitivity analysis to consider the Missingness Not At Random (MNAR) mechanism for monotone missing data. The mean change from baseline in LDH level at Week 26 will be analyzed based on the data observed while the subject remains on study treatment as well as the data imputed using multiple imputation (MI) methodology for the time points with missing values. Imputation of outcome values in the SOC group will rely on the MAR assumption. Imputation of the primary outcome values in the pegcetacoplan group will be done as if the subject had been on SOC. Imputed values in the pegcetacoplan group will be sampled using the imputation model of the SOC, i.e., conditional on the outcome values observed at the time points prior to discontinuation. This approach does not assume a sustained benefit of pegcetacoplan after discontinuation but rather assumes a post-discontinuation effect like that of SOC and time effects based the estimated correlations among the time points in the SOC group. The number of imputations will be 500 (NIMPUTE=500) and the random seed will be 123876 for both partial imputation and sequential regression imputation detailed in Steps 1 and 2. The approach will be implemented as follows:

- Step 1: Non-monotone missing data will be imputed first based on the MAR assumption and a multivariate joint Gaussian imputation model using the Markov chain Monte Carlo (MCMC) method using the MCMC statement in PROC MI. As a result, each imputed data set will only have missing data at the end of each subject's record, i.e., a monotone missing data pattern. The MCMC method in PROC MI will be invoked with multiple chains (CHAIN=MULTIPLE), 200 burn-in iterations and a non-informative prior. A separate imputation model will be used for each treatment group. The imputation models will represent a simplified version of the primary analysis model and will include the following terms: stratification variables, baseline LDH level and LDH levels at each time point. In case of non-convergence or other issues, a ridge prior and a single imputation model will be considered with the treatment term added to the model.

- Step 2: The resulting monotone missing data for all subjects who discontinue study treatment early will be imputed using a sequential regression multiple imputation model estimated based on the data from the SOC group only. Each sequential regression model for imputation of outcome values at a given time point will include the following terms: stratification variables, baseline Hb level and Hb levels at all previous time points. Missing values at a given time point in both treatment groups will be imputed from the same imputation model, conditional on the subject values observed or imputed at previous time points.

- Step 3: The change from baseline in Hb level to each scheduled post-baseline visit will be calculated based on the observed and imputed data. Each of the 1000 imputed complete data sets from Step 2 will be analyzed using the primary analysis model.
- Step 4: The results obtained in each imputed data set, including the treatment differences and their standard errors, will be combined using Rubin's imputation rules (Rubin, 1987) to produce a pooled estimate of the treatment differences, corresponding 95% confidence interval and a pooled treatment effect P-value using PROC MIANALYZE.

2- Imputation based on the delta-adjusted stress testing method

In addition to the control-based imputation method, sensitivity to departures from the MAR assumption will also be investigated using a tipping point analysis based on the delta-adjusted stress testing method. Departures from MAR in the pegcetacoplan group will be evaluated assuming that subjects who discontinue study treatment have, on average, efficacy outcomes after discontinuation that are worse by a pre-defined amount (delta) compared to the value which would have been assumed under an MAR model.

A series of analyses based on this method will be performed with increasing values of the delta until the treatment difference is no longer statistically significant. The smallest value of the delta parameter that overturns the primary conclusions is known as a tipping point. An interpretation of clinical plausibility of the assumptions underlying the tipping point will be provided.

The mean change from baseline in LDH level at Week 26 will be analyzed based on the data observed while a subject remains on study treatment as well as the data imputed using MI methodology for the time points with missing primary outcome values. Imputed values in the pegcetacoplan group will first be sampled from an MAR-based multiple imputation model and then the delta-adjusted method described will be applied as described below. The analyses will be performed using the delta starting from 0 with decrement of 0.2 until the null hypothesis can no longer be rejected.

As with the control-based imputation method, this approach uses MCMC for partial imputation of non-monotone data under MAR followed by sequential MI regression for monotone data.

- Step 1: The step is equivalent to the corresponding step for the control-based imputation method for non-monotone missing data (see Step 1).
- Step 2: The resulting monotone missing data will be imputed using sequential regression multiple imputation, where a separate regression model is estimated for imputation of outcome values at each time point. Each regression model will include the following terms: stratification variables, baseline Hb level and Hb

levels at all previous time points. The delta adjustment will be imposed on all imputed values at each visit after generating all imputations under the MAR assumption.

- Steps 3 and 4: The steps are equivalent to the corresponding steps for the control-based imputation method (see Steps 3 and 4).

17.4 COVID-19 Changes

The COVID-19 pandemic may impact the conduct of clinical trials such as site or laboratory closures, travel limitations, interruptions to the supply chain for the investigational product, or other considerations if site personnel or trial subjects become infected with COVID-19. Therefore, there is a possibility that we will have several missed visits by subjects and/or subjects might be referred to a certified local laboratory for blood works instead of central laboratory.

As a result of the COVID-19 global pandemic, Apellis issued an Urgent Safety Measure to safeguard the rights, welfare, and safety of APL2-308 study subjects and investigative site staff. These measures align with current guidance issued by global regulatory health authorities in regards to the impact of COVID-19 on the management of clinical trials.

The urgent safety measures are **minimum** study requirements and are reflected in the Schedule of Events table below and it supersedes the Schedule of Events table sent on 26 March 2020. A subject cannot be considered for screening using the minimum study requirements. The screening and baseline assessments must remain unchanged and must be completed in their entirety.

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

All assessments missed as a result of COVID-19 will be captured in the CRFs.

TRANSITION TO STUDY APL2-307

As per protocol, any subject that is able to travel to the study site and complete Week 26 of the APL2-308 study should transition over to Study APL2-307. However, the following modifications are allowed:

- Any subject that is not able to perform the Week 26 assessments on site due to COVID-19-related travel restrictions and/or site limitations, can remain on Study APL2-308 until such time as the restrictions are lifted or other options become available. Any subject that remains on Study APL2-308 should continue to follow the Week 26 visit schedule procedures and perform at least the minimum study requirements, in accordance with the Urgent Safety Measures, every 2 weeks until the transition to Study APL2-307 is possible.
- Any subject that is within 2 weeks of the Week 26 visit and is not subject to travel restrictions and/or study site limitations is encouraged to complete the Week 26 visit as soon as possible.

The CRA and medical monitor must be made aware of any subject who will not be able to complete the study transition or will be performing the Week 26 visit early.

While this decision may require subjects to stay in the APL2-308 study longer than anticipated, this decision will reduce subjects' need to travel during the ongoing pandemic.

This modification is also intended to ensure adequate study-related safety monitoring, continuity of investigational drug supply, reduction of subject travel and in-clinic time, and also to provide for more scheduling flexibility while maintaining study and data integrity.

Minimum Study Requirements

The following are the **minimum** study requirements for Study APL2-308 during the COVID-19 pandemic and should be used as guidance when the full protocol requirements cannot be conducted:

1. **Maintain** dosing schedules, considerations for escalation, and management per protocol
2. **Obtain** key safety laboratory assessments:
    a. All laboratory assessments should be drawn at the frequency required by the minimized Schedule of Events (provided below):
        i. Includes (at minimum): hematology with differential, reticulocyte count, chemistry, LDH, coagulation profile, and urine pregnancy test (only for women of childbearing potential)
    b. In the event that the clinical investigative site is closed and/or subjects are unable/unwilling to travel, subjects should be referred to a certified local laboratory that can perform the required safety testing (see Schedule of Events below). The investigator should collect the local laboratory reports, which must be redacted (eg, name and other local requirements), laboratory reference ranges, and file with the study records.
3. **Perform** minimal medical safety assessments:
    a. If the subject is unable to have an in-person assessment, the investigator (or delegated site staff) should have a telephone and/or video contact at a frequency noted in the protocol (at minimum) to solicit adverse events (including SAEs), transfusion requirements, and concomitant medications. The appropriate forms in the eCRF should be completed.
    b. All serious adverse events are still required to be reported to Apellis immediately and within 24 hours of the investigator becoming aware.
4. **Document** appropriate contact with the subject:

a. Earnest and reasonable attempts must be made to solicit adverse events and concomitant medications. The CRA and medical monitor must be notified of any subjects lost to follow-up.

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

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PPD Apellis Pharmaceuticals, Inc. Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 4/28/2021 9:44:24 AM Viewed: 4/28/2021 9:59:37 AM Signed: 4/28/2021 10:00:07 AM
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PPD Apellis Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 4/28/2021 9:44:23 AM Viewed: 4/28/2021 11:10:53 AM Signed: 4/28/2021 11:11:24 AM
Electronic Record and Signature Disclosure: PPD		

Signer Events	Signature	Timestamp
PPD Apellis Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 4/28/2021 9:44:23 AM Viewed: 4/28/2021 9:54:09 AM Signed: 4/28/2021 9:55:44 AM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
PPD Apellis Pharmaceuticals, Inc. Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 4/28/2021 9:44:23 AM Viewed: 4/28/2021 9:45:09 AM Signed: 4/28/2021 9:45:30 AM
Electronic Record and Signature Disclosure: PPD		
PPD Apellis Pharmaceuticals, Inc. Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 4/28/2021 9:44:23 AM Viewed: 4/28/2021 12:04:24 PM Signed: 4/28/2021 12:05:15 PM
Electronic Record and Signature Disclosure: PPD		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	4/28/2021 9:44:24 AM
Certified Delivered	Security Checked	4/28/2021 12:04:24 PM
Signing Complete	Security Checked	4/28/2021 12:05:15 PM
Completed	Security Checked	4/28/2021 12:05:15 PM

Payment Events	Status	Timestamps

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Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through your DocuSign user account all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact Apellis Pharmaceuticals, Inc. - Part 11:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: PPD

To advise Apellis Pharmaceuticals, Inc. - Part 11 of your new e-mail address

To let us know of a change in your e-mail address where we should send notices and disclosures electronically to you, you must send an email message to us at PPD and in the body of such request you must state: your previous e-mail address, your new e-mail address. We do not require any other information from you to change your email address..

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To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an e-mail to PPD and in the body of such request you must state your e-mail address, full name, US Postal address, and telephone number. We will bill you for any fees at that time, if any.
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i. decline to sign a document from within your DocuSign account, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an e-mail toPPD and in the body of such request you must state your e-mail, full name, IS Postal Address, telephone number, and account number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

Operating Systems:	Windows2000? or WindowsXP?
Browsers (for SENDERS):	Internet Explorer 6.0? or above
Browsers (for SIGNERS):	Internet Explorer 6.0?, Mozilla FireFox 1.0, NetScape 7.2 (or above)
Email:	Access to a valid email account
Screen Resolution:	800 x 600 minimum
Enabled Security Settings:	• Allow per session cookies

	• Users accessing the internet behind a Proxy Server must enable HTTP 1.1 settings via proxy connection

** These minimum requirements are subject to change. If these requirements change, we will provide you with an email message at the email address we have on file for you at that time providing you with the revised hardware and software requirements, at which time you will have the right to withdraw your consent.

Acknowledging your access and consent to receive materials electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please verify that you were able to read this electronic disclosure and that you also were able to print on paper or electronically save this page for your future reference and access or that you were able to e-mail this disclosure and consent to an address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format on the terms and conditions described above, please let us know by clicking the 'I agree' button below.

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