STATISTICAL ANALYSIS PLAN

APL-2
PHASE 3

A Phase 3, Randomized, Multi-Center, Open-Label, Active-Comparator Controlled Study to Evaluate the Efficacy and Safety of APL-2 in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)

PROTOCOL IDENTIFIER: APL2-302

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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
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
mITT	Modified ITT set
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
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 16 Aug 2019, incorporating the most recent amendment # 4. 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, ESTIMAND(S), AND ENDPOINTS

2.1 Objectives

The primary objectives of this study are to establish the efficacy and safety of APL-2 compared to eculizumab in subjects with paroxysmal nocturnal hemoglobinuria (PNH) who continue to have hemoglobin (Hb) levels <10.5 g/dL despite treatment with eculizumab.

2.2 Endpoints

2.2.1 Primary Endpoint

- Change from Baseline to Week 16, excluding data before the Randomized Controlled Period, in hemoglobin (Hb) level.

2.2.2 Key Secondary Endpoints

- Transfusion avoidance (TA) (Yes/No), defined as the proportion of subjects who do not require a transfusion during the Randomized Controlled Period.
- Change from Baseline to Week 16, excluding data before the Randomized Controlled Period, in reticulocyte count.
- Change from Baseline to Week 16, excluding data before the Randomized Controlled Period, in lactate dehydrogenase (LDH) level.
- Change from Baseline to Week 16, excluding data before the Randomized Controlled Period, in FACIT-fatigue scale score, Version 4.

2.2.3 Secondary Endpoints

- Hemoglobin response in the absence of transfusions (Yes/No). Hemoglobin response is defined as an increase of at least ≥1 g/dL in hemoglobin from Baseline at Week 16, excluding data before the Randomized Controlled Period.
- Reticulocyte normalization in the absence of transfusions (Yes/No). Reticulocyte normalization is defined as the reticulocyte count being below the upper limit of the normal range at Week 16.

- Hemoglobin normalization in the absence of transfusions (Yes/No). Hemoglobin normalization is defined as the hemoglobin level being above the lower limit of the normal range at Week 16.
- Change from Baseline to Week 16, excluding data before the Randomized Controlled Period, in indirect bilirubin level.
- Change from Baseline to Week 16, excluding data before the Randomized Controlled Period, in haptoglobin level.
- Change from Baseline to Week 16, excluding data before the Randomized Controlled Period, in LASA scores.
- Change from Baseline to Week 16, excluding data before the Randomized Controlled Period, in QLQ-C30 scores.
- Number of PRBC units transfused during the Randomized Controlled Period [> Day 1 to Week 16 and Week 4 to Week 16].
- Change from Baseline and change from Week 17 to Week 48 in hemoglobin level.
- Change from Baseline and change from Week 17 to Week 48 in reticulocyte count.
- Change from Baseline and change from Week 17 to Week 48 in lactate dehydrogenase (LDH) level.
- Change from Baseline and change from Week 17 to Week 48 in FACIT-fatigue scale score.
- Change from Baseline and change from Week 17 to Week 48 in LASA scores.
- Change from Baseline and change from Week 17 to Week 48 in QLQ-C30 scores.
- Number of PRBC units transfused during the Open-Label APL-2 Period [Week 17 to Week 48 and Week 20 to Week 48].

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 ECG parameters

2.2.5 Pharmacokinetic Endpoint

- APL-2 pharmacokinetic concentrations

2.2.6 Pharmacodynamics Endpoint(s)

- Change from Baseline to Week 16 and Week 48 in percentage of PNH Type II+III RBC cells opsonized with C3

- Change from Baseline to Week 16 and Week 48 in percentage of PNH Type II+III RBC cells
- Change from Baseline to Week 16 and Week 48 in complement (e.g., CH50, AH50, and C3) levels

The PD endpoints include 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:

- 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.

3. STUDY DESIGN

3.1 General Description

This is a prospective, Phase 3, randomized, multi-center, Open-label, active-comparator controlled study. A total of approximately 70 PNH subjects who are receiving eculizumab and who continue to have hemoglobin (Hb) levels <10.5 g/dL will be randomized to receive either APL-2 or eculizumab. The treatment Period of the study will consist of three parts:

- 4-week Run-in Period

- 16-week Randomized Controlled Period

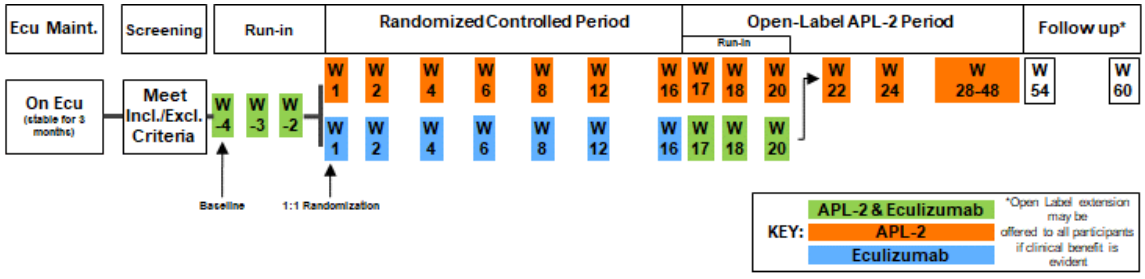
- 32-week Open-label APL-2 only Period (although subjects who receive eculizumab during the 16-week Randomized Controlled Period will continue to receive eculizumab for the first 4 weeks in addition to APL-2)

During the 4-week Run-in Period (Day - 28 to ≤ Day 1) all subjects will receive self-administered twice-weekly subcutaneous (SC) doses of APL-2 1,080 mg in addition to the subjects' current dose of eculizumab treatment, which will continue as prescribed regardless of study visit scheduling or the APL-2 administration schedule (i.e. it is not required that eculizumab dosing aligns with APL-2 dosing or APL2-302 study visits). On Day 1, subjects will receive their dose of APL-2 and may receive eculizumab depending on their dosing schedules. Subjects will then be randomized to either Group 1 (monotherapy APL-2) or Group 2 (monotherapy eculizumab). Subjects in Group 1 will receive APL-2, and subjects in Group 2 will receive eculizumab for the remainder of the 16-week Randomized Controlled Period. During the Randomized Controlled Period, subjects will return to the clinical site at Weeks 1, 2, 4, 6, 8, 12 and 16 for efficacy and safety assessments.

After completion of the Randomized Controlled Period (the end of Week 16), all subjects will continue into a 32-week Open-label APL-2 Period in which all subjects will receive twice-weekly doses of APL-2 1,080 mg. During this period, subjects will return to the clinical site on Weeks 17, 18, 20, 22 and 24 and every 4 weeks thereafter until Week 48 for efficacy and safety assessments. Those subjects who received eculizumab in the Randomized Controlled Period will receive APL-2 in addition to eculizumab for 4 weeks (Weeks 17-20).

After completion of the 52-week treatment Period (Week 48), subjects will be offered entry into an open-label extension study. Should the subject not enter the open label extension study they will exit the study and return to the site for 2 additional safety visits 6 weeks apart.

The study outline is displayed in the diagram below:



Subjects who withdraw from treatment prior to the Week 48 visit will be encouraged to continue their participation in the study and return to the study site for their scheduled study procedures, except for APL-2 administration. Subjects who withdraw from the

study prior to Week 48 and are currently being treated solely with APL-2 are recommended to receive at least one dose of eculizumab before discontinuing APL-2.

The planned length of participation in the study for each subject is a maximum of approximately 72 weeks, including an 8-week screening Period, 52-week treatment period and 12-week follow-up Period. Those who enter the open label extension study will not require the 12-week follow-up Period.

Subjects who fail the screening procedures should not be re-screened for the study unless this is agreed in advance and documented in writing with the sponsor.

3.2 Randomization

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

Subjects who meet all the eligibility criteria will be eligible to enter the 4-week Run-in Period. Following completion of the Run-in Period, subjects will be randomly assigned (1:1) using interactive response technology (IRT) to receive either 1,080mg of APL-2 twice-weekly or their current dose of eculizumab.

Initially the randomization was stratified by the following:

- Number of units of PRBC transfused within the 12 months prior to Day -28 (<3; ≥3)
- Platelet count at screening (<100,000; ≥100,000)

However, in Amendment 3 Version 1.0 of the protocol the stratification criteria were changed to:

- 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)
- Platelet count at screening (<100,000; ≥100,000)

For analysis purposes subjects will be re-assigned to stratification groups based on their actual data; any misallocations at randomization will be identified in a listing. The stratification groups used for analyses will be based on the groups introduced in Protocol Amendment 3 Version 1.0.

3.3 Sample Size and Power Considerations

A sample size of 64 randomized subjects (32 in each group) provides 90% power (using a 2-sided t-test at the 5% level of significance) of obtaining a statistically significant difference between the groups with the primary endpoint, Week 16 change from baseline in hemoglobin level. This assumes a treatment difference between APL-2 and eculizumab of 1 g/dL and a standard deviation for the change from baseline of 1.2 g/dL (effect size = 0.833). To account for loss of power due to discontinuations the study will attempt to randomize 70 subjects.

If the standard deviation is as high as 1.4g/dL the power is reduced to 80%. Consequently, a blinded sample size re-assessment may be performed prior to the completion of study enrolment. A statistician blinded to treatment assignment will estimate the standard deviation for the primary endpoint and determine the sample size required to maintain the power for the study. This assessment will not lead to a reduction in the sample size. The sample size of the study may be increased to a maximum of 100. An increase beyond this maximum would require a protocol amendment.

It is anticipated that more than 70 subjects will need to enter the Run-in Period to achieve 70 randomized subjects.

4. STATISTICAL ANALYSIS SETS

4.1 Screened Set

The Screened set will include all subjects who signed the informed consent form. This set will only be used for the purposes of describing the subject disposition and for listing the data.

4.2 Run-in Set

The Run-in set will include all subjects who receive at least one dose of APL-2.

4.3 Intent-to-Treat Set

The Intent-to-Treat (ITT) set will include all subjects who were randomized. The analyses using this set will be based upon the randomized treatment group allocated.

4.4 Safety Set

The Safety set will include all subjects who were randomized and received at least 1 dose of monotherapy study drug. This set will be used for safety analyses. The analyses using this set will be based upon the actual treatment received.

4.5 Modified ITT Set

The modified ITT (mITT) set will include all subjects in the ITT set who receive at least one dose of monotherapy beyond their Week 4 after randomization in the Randomized Controlled Period. The analyses using this set will be based upon the randomized treatment group allocated.

4.6 Per-protocol Set

The Per-protocol **(**PP) set will include all subjects in the ITT set who have not violated any inclusion or exclusion criteria and/or deviated from the protocol in a way that could influence their efficacy assessment. Decisions concerning the exclusion of subjects from this set will be made and documented prior to database lock. Subjects will be required to receive their randomized treatment to be included in the set and so analyses using this set will by default be based upon the actual treatment group allocated.

4.7 Completers Set

The Completers set will consist of all subjects in the ITT set who have completed the Week 16 efficacy assessment for the study. The analyses using this set will be based upon the randomized treatment group allocated.

4.8 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 important 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.

4.9 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 important 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 Run-in set, the following will be presented:

- Number and percentage of subjects who receive at least 1 dose of APL-2
- Number and percentage of subjects who completed the Run-in Period and were randomized
- Number and percentage of subjects who completed the Run-in Period and were not randomized (identified as completing treatment until their Study Visit 5 [Study Day 1])
- Number and percentage of subjects withdrawn from the study during the Run-in Period and reason for withdrawal

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 (APL-2 or eculizumab, and total)
- Number and percentage of subjects who completed study treatment
- Number and percentage of subjects who discontinued study treatment

For those subjects who discontinue study treatment, the reason for discontinuation will be summarized for each of the following study periods:

  - Day -28 to ≤ Day 1 (Run-in Period)
  - > Day 1 to Week 16 (Randomized Controlled Period)
  - > Week 16 to Week 20 (Open-label Run-in Period)
  - > Week 20 to Week 48 (Open-label Period)
- 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

The number of subjects in each analysis set will be tabulated overall and by country or region (North America, Europe, 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, mITT and Safety sets (if sets are different).

Demographic variables to be presented include age (years), age category (≤65 years and > 65 years), sex, race, ethnicity, country, 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 present using Run-in set include the following:

- Time since diagnosis of PNH (years) to Day -28
- Duration of treatment with eculizumab to Day -28
- Current eculizumab dose level and dosing regimen
- Number of transfusions in the last 12 months prior to Day -28
- Number of transfusions in the last 12 months prior to Day -28 (<4; ≥4)
- Platelet count at screening (<100,000; ≥100,000)
- Time since last transfusion to Day -28
- Hemoglobin level (average of values recorded prior to dosing with APL-2)
- Reticulocyte count (average of values recorded prior to dosing with APL-2)
- LDH level (average of values recorded prior to dosing with APL-2)
- Haptoglobin level (average of values recorded prior to dosing with APL-2)
- Total bilirubin level (average of values recorded prior to dosing with APL-2)
- Indirect bilirubin level (average of values recorded prior to dosing with APL-2)
- Total FACIT-fatigue score (nominally recorded on Day -28 prior to dosing with APL-2)

The average baseline value for hemoglobin (Hb) will include local and central laboratory 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.

5.3 Medical and Thrombosis History

Medical history will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) Version available. Summaries will be presented for the Run-in 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 Run-in set with numbers and percentages for each type of thrombosis by treatment group and overall.

5.4 Prior Therapies, Procedures and Medication

Prior and concomitant medications will be coded using the latest 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 will be defined as those medications started prior to the administration of APL-2 on Day -28. Concomitant medications will be defined as those medications taken following administration of APL-2 on Day -28. Hence medications started before receiving APL-2 but continuing after will be considered as both prior and concomitant medications. The listing of medications will identify prior and concomitant medications.

Prior procedure and intervention will be presented similar to those of prior medications detailed above.

Prior medications will be summarized using the Run-in set and be presented by treatment group (APL-2/ eculizumab and non-randomized (if any)) and overall.

5.5 Concomitant Medications

Concomitant medications will be summarized for different periods of the study:

Study Period	Analysis Set	Treatment Groups
Run-in	Run-in	APL-2 (up to Day 1 (≤ Day 1) / Eculizumab (up to Day 1 (≤ Day 1)) Non-randomized (up to the end of study [if any]) Overall
Randomized	Safety	APL-2 (up to Week 16*) Eculizumab (up to Week 16*) Overall
Randomized and Open-label	Safety	APL-2 Eculizumab Overall

* or end of study for those who do not complete Week 16

5.6 Exposure to Investigational Product

The following parameters will be calculated and presented by treatment group for the Run-in Period (Day -28 to ≤ Day 1), Randomized controlled Period (> Day 1 to Week 16) and Open-label Period (Week 17 to Week 48) periods 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 received only1, 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.

The treatment duration for the Open-label Period will also be calculated and summarized separately.
Number of infusions for each subject will summarized using descriptive statistics.

5.7 Measurements of Treatment Compliance

Percent compliance will be calculated for the Randomized Controlled Period using the safety set as follow:

Percent compliance = total number of study infusions taken from Day 2 to end of Randomization Controlled Period (Week 16) / total number of expected infusions to end of Randomization Controlled Period.

The number and percentage of subjects who had a percentage of drug compliance range by increment of 10% (≥ 80% - 90% and ≥ 90 - ≤100%) will then be presented in a table by treatment group.

The number of expected doses will be different between the two groups in the Randomized Controlled Period as it will be 32 to 37 doses for APL-2 twice weekly or every 3 days and 8 doses for eculizumab q2w.

Compliance will also be calculated and summarized by treatment group for the Run-in and the Open-label Periods using the calculation shown above.

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

5.8 Protocol Deviations

All protocol deviations will be reviewed and documented before database lock. Protocol deviations are being captured in the clinical database by the site staff. They may also be identified through programmable checks of the data.

Key protocol deviations include any violations of inclusion and exclusion criteria. This includes unknown violations at enrolment and on-study violations, such as taking a prohibited medication.

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.

6. EFFICACY ANALYSES

Unless otherwise specified, baseline for all efficacy analyses is defined as the average of measurements recorded prior to taking the first dose of investigational product (i.e. prior to the start of the Run-in Period (Day -28)).

All confidence intervals (CI) will be 2-sided 95% confidence intervals. All statistical superiority tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects.

For non-inferiority tests, non-inferiority will be concluded if the appropriate limit of the 95% confidence interval indicates APL-2 is no inferior than eculizumab by the defined non-inferiority margin for each applicable efficacy parameter as detailed below in the section of key secondary endpoints. This is equivalent to a 1-sided hypothesis test at the 2.5% significance level.

Summary Tables

Absolute values and changes from baseline will be summarized by treatment group and visit within each of the periods of the study.

For categorical data, the number and percentage will be summarized by treatment group and visit within each of the periods of the study.

If a subject has a transfusion during the Randomized Controlled Period, their data collected after the transfusion will be excluded from the calculation of descriptive statistics for all efficacy 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 percentages will be presented and summarized in a table.

Additional summary tables will be generated whereby data collected after the transfusion will be included in the calculation of descriptive statistics for all efficacy endpoints other than hemoglobin.

For the Run-in Period, Open-label Period and overall, observed data will be summarized by three treatment group (APL-2, eculizumab, and non-randomized [if any]) and for Randomized Controlled Period by two treatment group (APL-2 and eculizumab).

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 criteria.

6.1 Estimands

- The primary objective is to compare APL-2 and Eculizumab at week 16 assuming that the subjects continue the assigned treatment as directed.
- The intercurrent events (ICE) that will be considered are:
    1. Transfusions
    2. Discontinuation of Study Treatment
    3. Withdrawal from the study

Transfusions

With this study population it is likely that some subjects who are not having their hemolysis suitably controlled by study medication will have a drop in Hb during the 16 weeks of Randomized Controlled Period and require a red blood cell transfusion. However, it would be scientifically unsound to use data collected after the transfusion in efficacy analyses for the study. Consequently, for any subject who receives a transfusion (per the transfusion criteria listed in Section 12.7.1 of the protocol), all subsequent values will be set to missing for the following measurements (While on-Treatment Strategy):

- Hemoglobin count
- Reticulocyte count
- LDH level
- Bilirubin level
- Haptoglobin level
- FACIT-fatigue scale score
- LASA scores
- QLQ-C30 scores

Discontinuation of Study Treatment

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

Withdrawal from the Study

This situation will be handled in the same way as described for transfusions above (While on Treatment Strategy).

The following table shows the primary Estimands and the sensitivity and the supportive analyses for the primary efficacy endpoint:

Definition	Attributes			
The effect APL-2 compared to eculizumab on Hb levels after 16 weeks of monotherapy treatment to PNH subjects	**A: Population**	**B: Variable (or endpoint)**	**C: Strategy for addressing intercurrent event (ICE)**	**D: Population-level summary**
	ITT	Week 16 Hb change from baseline	• For transfusion and withdrawal from the study: all measurements after the ICE events will be set to missing (while on-treatment strategy) • For discontinuation of treatment: all measurements after discontinuation will be used in the analyses (treatment strategy)	Difference between treatment means with 95% confidence interval
	Sensitivity Analyses			
	ITT	Week 16 Hb change from baseline	Controlled-Based Pattern Imputation	Difference between treatment means with 95% confidence interval
	ITT	Week 16 Hb change from baseline	Imputation based on the delta-adjusted stress testing method (Tipping Point)	Difference between treatment means with 95% confidence interval
	Supportive Analyses			
	PP	Week 16 Hb change from baseline	Same as primary endpoint ICE criteria.	Difference between treatment means with 95% confidence interval
	mITT	Week 16 Hb change from baseline	Same as primary endpoint ICE criteria.	Difference between treatment means with 95% confidence interval
	ITT	Week 16 Hb change from baseline	Use all available data. i.e. not setting values to missing after transfusions	Difference between treatment means with 95% confidence interval

	ITT subjects who complete the study	Week 16 Hb change from baseline	Use all available data.	Difference between treatment means with 95% confidence interval
	ITT	Hb Change from baseline	• Last Hb Level before ICE for subject with ICE. • Last available Hb level for subject without ICE.	Difference between treatment means with 95% confidence interval based on nonparametric randomization-based ANCOVA

6.2 Analyses of Primary Efficacy Endpoint

6.2.1 Primary Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in Hb level at Week 16 of the Randomized Controlled Period. If a subject receives a transfusion during the randomized Controlled Period or withdraws from the study, the Hb levels up to the transfusion or time of withdrawal will be included in the model. If subject receives transfusion, the pre transfusion Hb value from the local laboratory will be used, however, if it is not collected or missing, then the pre transfusion central laboratory Hb value will be used.

The between-treatment group comparison for the 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 platelet count) and the study visit-by-treatment group interaction, as well as the continuous, fixed covariate of baseline Hb level. Initially an unstructured covariance matrix will be investigated. If this analysis fails to converge, other structure will be tested, and the final covariance structure will be determined using the Akaike's information criteria. The Kenward Roger's approximation will be used to estimate denominator degrees of freedom.

The difference between APL-2 and eculizumab mean Hb changes from baseline at Week 16 will be calculated along with its 2-sided 95% CI and associated P-value from the MMRM model.

6.2.2 Sensitivity Analyses of Primary Efficacy Endpoint

The primary analysis model relies on the assumption of Missingness At Random (MAR). According to this assumption, the unobserved outcome values for subjects who discontinue study treatment early are considered to be similar to the observed outcome values in subjects with similar history assigned to the same treatment group. In other words, the distribution of the unobserved future outcomes for subjects who discontinue study treatment is the same as the distribution of the observed outcomes for those who continue treatment, conditional on the available data prior to discontinuation.

Additional analyses that reflect possible lack of treatment benefits following a subject's discontinuation from study treatment will be performed using the following methods:

1- Control-based pattern imputation method using the data up to ICE.

2- Imputation based on the delta-adjusted stress testing (Tipping Point) method using the data up to ICE.

These methods can be considered as sensitivity analyses for the primary MAR based analysis 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 control-based multiple imputation sensitivity analysis will consider a certain type of the MNAR mechanism for the missing data within the pattern-mixture framework, where it will be assumed that subjects who discontinue early from the APL-2 group will follow the trajectory of outcomes similar to the one in the Eculizumab group after their discontinuation, taking into account the observed values prior to discontinuation (Ratitch et al., 2013). Subjects who discontinue early from the Eculizumab group will be assumed to have unobserved outcomes similar to other Eculizumab subjects who remain in the Eculizumab group (see Appendix 17.3).

The second 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 APL-2 group experience worsening defined by a pre-specified adjustment in the primary efficacy endpoint (mean Hb change from baseline at Week 16). After the initial imputation, a range of shifts will be added to the imputed missing data in both APL-2 and Eculizumab groups.

The details are provided in the Appendix 17.3.

6.2.3 Supportive Analyses of Primary Efficacy Endpoint

The following supportive analyses will be provided for the primary endpoints:

- an MMRM analysis using the PP set using data up to ICE
- an MMRM analysis using the mITT set using all available data after Week 4.
- an MMRM analysis using all available data from the ITT set, regardless of whether the Hb measurement was following a transfusion.
- an MMRM analysis using the completers set using data up to ICE.
- Nonparametric Randomization-Based ANCOVA using ITT set using the data specified below.

The difference between APL-2 and Eculizumab in mean Hb changes from baseline at Week 16 will be calculated along with its 2-sided 95% CI.

For the nonparametric randomization-based ANCOVA analysis, the endpoint will be the rank of the change from baseline in Hb level. The Hb level is defined as follow:

- Last Hb Level before ICE for subject with ICE.
- Last available Hb level for subject without ICE.

The between-treatment group comparison for the rank-based primary efficacy endpoint will be performed using an Analysis of Covariance (ANCOVA). The model will include fixed categorical effects for treatment group, and stratification variables (based on transfusion history and platelet count).

6.3 Analyses of Key Secondary Efficacy Endpoints

The analyses of key secondary efficacy endpoints are based on non-inferiority tests. Non-inferiority will be concluded if the appropriate limit of the 95% 2-sided confidence interval indicates APL-2 is not inferior to eculizumab by the defined non-inferiority margin for each key secondary efficacy endpoints as detailed below (section 6.3.2).

Once the non-inferiority is established for the key secondary endpoints, then superiority will be assessed for transfusion avoidance, change from Baseline to Week 16 in reticulocyte count and change from Baseline to Week 16 in FACIT-fatigue score using a closed-testing procedure at a significance level of 0.05.

6.3.1 Transfusion Avoidance

The number and percentage of subjects in the following categories will be presented by treatment group:

- no transfusions over the Randomized Controlled Period (> Day 1 to Week 16)
- receive a transfusion during the Randomized Controlled Period
- withdrew from the study without having had a transfusion during the Randomized Controlled Period

Subjects who have not had a transfusion but withdraw before Week 16 will be considered as having a transfusion in the analysis of transfusion avoidance.
The number and percentage of subjects with transfusion avoidance will be tabulated by treatment group and compared between treatment groups using a stratified Cochran-

Mantel Haenszel (CMH) chi-square test. The treatment difference in percentages and 95% confidence interval for the difference will be presented using the stratified (Miettinen, 1985) method.

If the lower bound of the 95% CI for the difference between APL-2 and eculizumab treatment groups is greater than the non-inferiority margin of -20%, then APL-2 will be considered non-inferior to eculizumab.

6.3.2 Continuous Key Secondary Endpoints

Change from Baseline Endpoints

The absolute values and changes from baseline in reticulocyte count, LDH level and FACIT-fatigues scale score will be summarized by treatment group at Baseline and each study visit.

The change from baseline at Week 16 in reticulocyte count, LDH level and FACIT-fatigue scale score will be analyzed using the same methods described for the primary analysis of the primary efficacy endpoint except using their own baseline as a covariate, using the ITT and mITT sets.

For reticulocyte count, if the upper bound of the 95% CI for the treatment difference is less than the non-inferiority margin of 10, then APL-2 will be considered non-inferior to eculizumab.

For LDH, if the upper bound of the 95% CI for the treatment difference is less than the non-inferiority margin of 20, then APL-2 will be considered non-inferior to eculizumab.

For FACIT-fatigue score, if the lower bound of the 95% CI for the treatment difference is greater than the non-inferiority margin of -3 then APL-2 will be considered non-inferior to eculizumab.

6.3.3 Categorization of FACIT-Fatigue Scores

The FACIT-fatigue scores will be categorized and the proportion of subjects with an improvement of at least 3 points for the FACIT-fatigue scores from baseline will be summarized by treatment group and by visit using the ITT and mITT sets.

6.3.4 Supportive Analyses of Key Secondary Efficacy Endpoints

The key secondary endpoints will also be analyzed using the PP set.

The analyses for the key continuous secondary endpoints will be repeated using all available data.

6.4 Analyses of Secondary Efficacy Endpoints

6.4.1 Randomized Control Period

6.4.1.1 Categorical Secondary Efficacy Endpoints

The number and percentage of subjects meeting the following criteria will be tabulated by treatment group at Week 16 and the superiority test will be used to compare the 2 treatment group:

- Hemoglobin response (≥ 1 g/dL increase from baseline in the absence of transfusion)
- Reticulocyte normalization (≤ ULN)
- Hemoglobin normalization (≥ LLN)

Also, the number and percentage of subjects in the following categories will be presented by treatment group:

- receive a transfusion during the Randomized Controlled Period
- withdrew from the study before Week 16

The hemoglobin response, reticulocyte normalization and hemoglobin normalization responder endpoints are binary responses (i.e., Yes vs. No); each endpoint will be analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factors at randomization. The odds ratio of being a responder (Yes) on each of the endpoints for the APL-2 vs. eculizumab and associated 95% confidence interval (CI) will be provided. Subjects who received a transfusion between Day 2 and Week 16 or withdraw without providing efficacy data at Week 16 will be classified as non-responders in these endpoint's primary analysis.

Additionally, the proportion of responders based on each of the key secondary endpoints (Hemoglobin response, Reticulocyte normalization, Hemoglobin normalization , and absence of transfusion) for each treatment group will be summarized, and their respective 95% CI using the stratified (Miettinen, 1985)method will be reported. The

difference in the proportion of responders between the 2 treatment groups and the corresponding 95% CI will also be summarized.

6.4.1.2 Continuous Secondary Efficacy Endpoints

Change from Baseline Endpoints

Superiority will be assessed for the change from baseline to week 16 for the continuous secondary endpoints

The absolute values and changes from baseline in indirect and total bilirubin level, haptoglobin level, LASA scores and QLQ-C30 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 16 in indirect bilirubin level, haptoglobin level, LASA scores and QLQ-C30 scores will be analyzed using the same methods described for the primary analysis of the primary endpoint, except using their own baseline as a covariate. The ITT and mITT sets will be used.

Number of PRBC units and Number of Transfusions

The number of PRBC is reported in units and mL in the database, therefore, the mL will be converted to units using the following formula:

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

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 16 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 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.

Normalized LDH to ULN (i.e. LDH Value/ ULN) will be computed and summarized by treatment group and by visit.

6.4.2 Open-Label Period

Absolute values and changes from baseline from Week 17 up to Week 48 will only summarized using ITT set in the following parameters by treatment group at each study visit. Missing scores during the Open-label Period will not be imputed.

- hemoglobin level
- reticulocyte count
- lactate dehydrogenase (LDH) level
- Total and indirect Bilirubin
- haptoglobin
- FACIT-fatigue scale score
- LASA scores
- QLQ-C30 scores

Number of PRBC units transfused during the Open-Label APL-2 Period will be summarized.

In addition, Week 48 shift from Week 16 tables will also be produced for hemoglobin count, reticulocyte level and LDH. The number and percentage of subjects will be tabulated by treatment group using the following categories for normalization (≤ ULN for reticulocytes and LDH, and ≥ LLN for hemoglobin) of each parameter:

Week 16 categories

- Normalized at Week 16
- Not normalized at Week 16

- Transfusion during the Randomized Controlled Period
- Withdrew prior to Week 16

Week 48 categories

- Normalized at Week 48
- Not normalized at Week 48
- Transfusion during the Open-label Period
- Withdrew prior to Week 48

A similar table will be produced for hemoglobin response (≥ 1 g/dL increase from baseline). Marginal totals and percentages will be included.

6.5 Multiplicity Adjustment

To preserve the Type 1 error rate, the key secondary endpoints will be tested in a hierarchical manner after statistical significance is reached for the primary endpoint. Once one hypothesis is tested not significant, all subsequent tests will not be assessed. Estimates will be computed for all key secondary and secondary endpoints regardless of whether a hypothesis is tested not significant preventing assessment of subsequent tests.

1) Transfusion avoidance (TA) – non-inferiority (NI) test (2.5% level) using a NI margin of -20% for the difference between proportions.

2) Change from Baseline to Week 16 in reticulocyte count – NI test (2.5% level) using a NI margin of +10

3) Change from Baseline to Week 16 in LDH – NI test (2.5% level) using a NI margin of +20

4) Change from Baseline to Week 16 in FACIT-fatigue score – NI test (2.5% level) using a NI margin of -3

Once the non-inferiority is established for the key secondary endpoints, superiority will be assessed in a hierarchical manner using a two-sided test at significance level of 0.05 for the following key secondary endpoints:

5. Transfusion avoidance

6. Change from Baseline to Week 16 in reticulocyte count.

7. Change from Baseline to Week 16 in FACIT-fatigue score.

6.6 Subgroup Analyses

The primary and key secondary endpoints will be summarized and analyzed by the following subgroups:

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- Platelet count at screening (<100,000; ≥100,000)

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

7. SAFETY ANALYSIS

The safety analysis will be performed using the Run-in and Safety Sets. 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 16 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 latest Version of MedDRA.

An AE (classified by preferred term) that occurs during the study will be considered a TEAE if it has a start date on or after the first dose of investigational product or if it has a start date before the date of the first dose, 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 30 days 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 each Period of the study.

For the Run-in Period of the study the number and percentage of subjects, Total events, and Total unique events (Run-in set) who have the following will be tabulated by 2 treatment groups (APL-2/eculizumab and non-randomized (if any)) and overall:

- any TEAE
- any TEAE considered as related to APL-2 (evaluated by the investigator as definitely related, possibly related)
- any TEAE considered as related to eculizumab (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

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 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.

Similar tabulations will be presented for TEAEs in the Randomized Controlled and Open-label Periods, except that:

- the Safety set will be used, and
- tabulations will be by the 2 treatment groups (APL-2 and eculizumab)

In addition to having the tabulations by study Period, data will also be summarized over the whole study for APL-2 and eculizumab up to 30 days beyond the last dose of study medication.

For the Run-in Period (Day1 to Week 4) and the post-Run-in Period (Week 4 to Week 16) within the Randomized Controlled Period, an additional table will be created as supportive analyses to present and compare the TEAEs by treatment group (ALP-2 and eculizumab) using the Safety set.

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 study Period, 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.

A separate listing of serious AEs will also be generated.

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

7.2 Clinical Laboratory Data

Descriptive statistics for clinical laboratory values (in SI units) and changes from baseline for each Period 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 range at every visit and the following categories will be derived for the shift tables (below N-R, Normal, Above N-R, and undetermined).

In case of using local laboratory with different normal ranges for Hb levels pre transfusion, the method developed by (Stein, 1992) may be utilized to normalize the Hb data for the purpose of analyses. If, however, the Hb normal ranges for all laboratories are close to each other, a global Hb normal range may be created to be used for analyses.

Clinical laboratory test values are potentially clinically significant () 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		1,5	1
Moderate		1	0.5
Severe		< 0.5	
Platelets levels	10^9/L		
Mild		150	100
Moderate		100	50
Severe		< 50	

All laboratory data will be listed for the Run-in and Safety Sets. 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 will be listed for the Run-in and Safety Sets. The listing will include change from baseline values

7.4 Electrocardiogram (ECG)

QT Analyses will be performed by ERT and the results will be delivered to Apellis in a separate data. 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 Run-in set for Run-in Period and 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), where applicable, will be summarized by treatment group.

8. PHARMACOKINETIC ANALYSIS

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

APL-2 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 APL-2 concentrations will be evaluated using the PK analysis set. APL-2 concentrations will be summarized by treatment group (relevant as eculizumab Randomized subjects will receive APL-2 during the Run-in and Open-label Periods) at each scheduled time point using descriptive statistics. The 6-hour post dose concentrations will only be included in the calculation of summary statistics if within a ±30 minute window of 6 hours after dosing. All other samples, except follow-up samples, are to be taken pre-dose. If a subject discontinues APL-2 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 APL-2 dose.

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

Linear and log-linear mean (± SE) concentration profile plots against time will be produced for each treatment group. The actual sampling time will be used on the x-axis. Plots will be presented for the full profile (Day -28 to Day 420).

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 an APL-2 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 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 16 and Week 48 in percentage of PNH Type II+III RBC cells opsonized with C3
- Change from Baseline to Week 16 and Week 48 in percentage of PNH Type II+III RBC cells
- Change from Baseline to Week 16 and Week 48 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:

- 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.

Mean 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. Plots will be presented for the full profile (Day -28 to Day 420).

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 formal interim analyses are planned for the primary endpoint, however data from the first 16 weeks will be reported once all subjects have completed their Week 16 visit or discontinued prior to Week 16 and the database has been cleaned for all visits up to and including Week 16.

12. DATA MONITORING COMMITTEE/REVIEW COMMITTEE

A DMC will be set up to review only the safety and tolerability data during the trial, and no formal reviews for efficacy will be performed. The DMC charter will be prepared in a separate document. The first DMC meeting will be scheduled 3 months after the first subject is randomized, and approximately at 6-month intervals, thereafter.

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 start of APL-2 treatment (nominally Day -28) for efficacy endpoints, but as the last measurement before the first dose of APL-2 for other endpoints.

The average baseline value for hemoglobin (Hb) will include 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 2. The date of randomization has been chosen as Day 2 as subjects in the eculizumab group may not have their first Randomized eculizumab dose until a few days after randomization.

13.3.1 Efficacy Summary Tables, Figures and Listings

Absolute values and changes from baseline will be summarized by treatment group and visit within each of the Periods of the study.

If a subject has a transfusion their data collected after the transfusion will be excluded from the calculation of descriptive statistics for all efficacy endpoints.

The number and percentage of subjects meeting the following criteria will also be tabulated by treatment group, for each visit:

- Hemoglobin response (≥ 1 g/dL increase from baseline)
- Hemoglobin normalization (≥ LLN)
- Reticulocyte normalization (≤ ULN)

- LDH normalization (≤ ULN)

For the Run-in and Open-label Periods observed data will be summarized by treatment group (2 groups for the Run-in Period (APL-2/ Eculizumab, and non-Randomized (if any)) and 2 groups (APL-2 and Eculizumab) for the Open-label Period) and overall.

Plots of Continuous Variables

Mean (± SE) plots will be displayed for each Period of the study separately.

The plots will be presented by treatment group using the means derived from the summaries mentioned above.

Listings

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

13.4 Treatment Labels

Summary tables covering visits during the 16-week Randomized Controlled Period will be presented by treatment group. The labels to be used in TFLs will be:

- APL-2
- Eculizumab

Summaries covering visits during the Screening, 4-week Run-in and 32-week Open-label Periods will be presented by treatment group and overall subjects. Some subjects may not progress into the Randomized Controlled Period from the Run-in Period; for summaries these will be assigned to a group with the label "Non-randomized".

13.5 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 while the relative day of each assessment will be calculated as [(date of assessment) – (date for randomization)] for prior to 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 the interval separating 2 scheduled visits is an even number of days, the middle day will be included in the lower bound of the next 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 1) will be assigned to the Run-in Period. See the table below for details on visit windows:

Part	Study Visit	Target Day	Analysis Window	Interval
S + Run-in	1	Up to -84	< -28	NA
	2	-28	≥-28 – ≤ -25	3
	3	-21	>-25 - ≤ -17	8
	4	-14	>-17 – 0	18 Asymmetric
	5 Day1 / Week 1	1	1	1
RCP				
	6 Week 2	14	>=2- ≤ 21	14
	7	28	21 – ≤ 35	14
	8	42	35 - ≤ 49	14
	9	56	49 - ≤ 69	20
	10	84	70 - ≤ 98	28
	11	112	98 - ≤ 116	8
O-L	12	119	116 - ≤ 123	6
	13	126	123 - ≤ 132	10
	14	140	133 - ≤ 147	14
	15	154	147 - ≤ 161	14
	16	168	161 – ≤ 175	14

Part	Study Visit	Target Day	Analysis Window	Interval
	17	196	175 –≤ 209	14
	18	224	210 - ≤ 238	28
	19	252	238 - ≤ 252	28
	20	280	252 - ≤ 280	28
	21	308	280 - ≤ 308	28
	22	336	308 - ≤ 336	28
	23	378	336 - ≤ 378	28
FU	24	420	378 - ≤ 420	28

13.6 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.

13.7 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.

13.8 Handling of Missing, Unused, and Spurious Data

13.8.1 Missing Data Imputation for Efficacy Endpoints

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

13.8.2 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. Missing Date Information for Prior or Concomitant Medications (Therapies/Procedures)

For prior or concomitant medications, including the rescue medication of eculizumab, 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 APL-2 dosing or missing) the date will be imputed as the first dose date of APL-2; 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.

13.8.2.1 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.

13.8.2.1.1 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.

13.8.2.1.2 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 13.8.2.1.1.

13.8.2.1.3 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.

13.8.2.2 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

13.8.2.2.1 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.

13.8.2.2.2 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.

13.8.2.2.3 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.

13.8.3 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 APL-2 dosing or missing) the date will be imputed as the first dose date of APL-2; 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.

13.8.3.1 Incomplete Start Date

Follow the same rules as in Section 13.8.2.1.2.

13.8.3.2 Incomplete Stop Date

Follow the same rules as in Section 13.8.2.2.

13.8.4 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.

13.8.5 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.

13.8.6 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

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

- The primary analysis specified in the protocol has been replaced by an MMRM analysis. The analysis specified in the protocol is not performed.
- The primary analyses of secondary endpoints using imputations for missing data and ANCOVA have been replaced by MMRM analyses.

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

Version 1.0 (dated 01 October 2019) of the SAP has been amended with the following changes:

- The estimand table was corrected to reflect the text in the Estimand section: change from the Hypothetical policy for the ICE to the while on-treatment strategy. This implies that all data for the primary and key secondary endpoints (ITT, mITT and PP sets) were set to missing after the first transfusion or if the subject discontinue the study.
- Per the FDA request, a supportive analysis using nonparametric randomization based ANCOVA analysis for the primary endpoint was added.
- Normalized LDH to ULN (i.e. LDH Value/ ULN) was added and will be computed and summarized by treatment group and by visit.
- For subject who receives transfusion, the pre transfusion Hb value from the local laboratory will be used, however, if it is not collected or missing, then the pre transfusion central laboratory Hb value will be used.
- All assessments that occur after Day 1 will be assigned to the Randomization controlled Period, whilst any assessment that occurs on or before to Day 1 (≤ Day 1) will be assigned to the Run-in Period.

- Analysis Window table was added.

- Additional supportive analyses for the key continuous secondary endpoints using all available data were added.

- Additional analyses for the number of units of PRBCs transfused and number of transfusions using log-incidence density ratios (non-parametric) were added.

3- Additional analyses for the key secondary endpoints by the Number of PRBC transfusions within the 12 months prior to Day -28 (<4; ≥4) and by Platelet count at screening (<100,000; ≥100,000) were added.

- Table for any TEAE infections, Serious Infections, and related infections was added.

16. REFERENCES

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17. APPENDICES

17.1 Schedule of Assessments

Study Period	Screening	Run-in Period			Randomized Controlled Period							Open-Label Period						Follow-Up
Study Week	up to -12[P]	-4	-3	-2	1	2	4	6	8	12	16	17	18	20	22	24	28, 32-48	54 & 60
Study Day	up to -84	-28	-21	-14	1	14	28	42	56	84	112	119	126	140	154	168	196, 224-336	378 & 420
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17-22	23 & 24
Clinic Visit Window (+/- Days)	N/A	2	2	2	0	2	2	2	2	2	2	2	2	2	2	2	7	7
Informed Consent	X																	
Demographics	X																	
Medical and thrombosis history	X																	
Transfusion history	X[Q]	X[Q]																
Inclusion/Exclusion[A]	X	X[A]																
Vaccination. [B]		X	X	X		X												
Physical examination. [C]	X	X			X						X						X	X
12-lead electrocardiogram. [D]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
APL-2 administration. [E]		Group 1 & 2			Group 1							Group 1 & 2						
Eculizumab treatment		Group 1 & 2[N]			Group 2[N]							Group 2[N]						

Study Period	Screening	Run-in Period			Randomized Controlled Period							Open-Label Period						Follow-Up
Study Week	**up to -12[P]**	**-4**	**-3**	**-2**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**17**	**18**	**20**	**22**	**24**	**28, 32-48**	**54 & 60**
Study Day	**up to -84**	**-28**	**-21**	**-14**	**1**	**14**	**28**	**42**	**56**	**84**	**112**	**119**	**126**	**140**	**154**	**168**	**196, 224-336**	**378 & 420**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17-22**	**23 & 24**
Clinic Visit Window (+/- Days)	**N/A**	**2**	**2**	**2**	**0**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**7**	**7**
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital sign measurements. [F]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[R]	X	X		X	X		X		X	X	X		X	X		X	X	X
Blood. [G, R]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics.[H]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-APL-2 Ab assay.[I]		X	X		X						X						X[I]	X
Direct Antibody Test (Coombs)	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
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
Coagulation profile.[J]		X			X				X		X					X	X[J]	X[J]
Complement profile (C3, CH50 and AH50)		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	Screening	Run-in Period			Randomized Controlled Period							Open-Label Period						Follow-Up
Study Week	**up to -12[P]**	**-4**	**-3**	**-2**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**17**	**18**	**20**	**22**	**24**	**28, 32-48**	**54 & 60**
Study Day	**up to -84**	**-28**	**-21**	**-14**	**1**	**14**	**28**	**42**	**56**	**84**	**112**	**119**	**126**	**140**	**154**	**168**	**196, 224-336**	**378 & 420**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17-22**	**23 & 24**
Clinic Visit Window (+/- Days)	**N/A**	**2**	**2**	**2**	**0**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**7**	**7**
Flow cytometry for PNH and C3 deposition	X	X		X	X	X	X		X	X	X		X	X	X	X	X	X
Plasma (free) Hb	X	X			X		X		X	X	X			X		X	X	X
Ferritin	X	X			X		X		X	X	X			X		X	X	X
Pregnancy (B-HCG) or FSH. [K]	X																	
Genotyping for Gilbert's Syndrome[L]	X																	
Urine pregnancy test. [M]		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	X	X	X	X	X	X
LASA Scale		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EORTC QLQ-C30 Questionnaire		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Investigational Product		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Return Investigational Product[O]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

FOOTNOTES:

A. Laboratory values from Screening will be used in addition to inclusion/exclusion criteria to confirm patient eligibility on Day -28.

B. If required; e.g., not previously-vaccinated subjects will receive vaccinations against *Neisseria meningitidis* types A, C, W, Y and B, *Streptococcus pneumoniae* and *Hemophilus influenzae* Type B (Hib). If the subject's first documented *Neisseria meningitidis* vaccine(s) are administered during the Run-in Period (Day -14), a booster (for both vaccinations) should be administered after 2 months. If Pneumococcal vaccination is required, please refer to Section 13.2.1 of the protocolfor vaccination scenarios. The PI will discuss with the Sponsor in regard to specific patient requirements.

C. Full physical examination will be performed at the D-28, D1, Wk16, Wk48 and Exit Visit. A symptom-driven physical examination may be performed at other times, at the PI's discretion.

D. Triplicate 12-lead electrocardiograms (ECGs) are to be performed pre-dose (-45, -30, and -15 minutes) and 6 hours post-dose on D-28, D1, Wk16 and Wk48. Triplicate 12-lead ECGs will be performed at all other visits (prior to dosing, if dosing will occur during the study visit).

E. Subjects will self-administer SC APL-2 twice weekly (or every 3 days subject to pre-approved dose adjustment), after receiving appropriate training by a research nurse or other personnel. Every subject will administer APL-2 at the study site through the Run-in Period (Visit 2-Visit 4) and at Visit 5 (Day 1). For subjects randomized to APL-2, following Visit 5 (Day 1), every effort should be made to ensure that the subject's APL-2 dosing schedule aligns with study visit days, and subjects should administer APL-2 at the study site and complete the post-administration study procedures. Details regarding APL-2 dosing during study visits can be found in Section 13 f the protocol.

F. Vital signs will be measured before venipuncture and ECG, vital signs measured post-dose will be timed from the completion of the study drug administration. Additional monitoring of vital signs will occur on D-28, D-25 (home or clinic visit), D1, Wk16 and Wk48 (pre-dose, 30 minutes, 2, 4 and 6 hours post-dose). At all other visits, if APL-2 and/or eculizumab is administered at the study site, vital signs will be measured pre-dose and 30 minutes post-dose.

G. Blood samples will be taken pre-dose (exception: see H below).

H. On D-28, D1, Wk16 and Wk48 only, pharmacokinetic samples will be taken pre-dose and at 6 hours (+/- 30 minutes) post-dose. PK samples will be taken pre-dose at all other visits.

I. Anti-APL-2 assay to be performed only on Week 32 and Week 48.

J. Coagulation profile to be completed only on Week 32, Week 48, and Week 60. The use of silica reagents in coagulation panels should be avoided in subjects treated with APL-2.

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

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

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

N. On Day 1, subjects will receive their last dose of APL-2 and may receive their last dose of eculizumab depending on their dosing schedule. During the Run-in Period for all subjects (Visit 2 [Week -4 (Day -28)] to Visit 4 [Week -2]) and through the Randomized Controlled Period for subjects randomized to eculizumab (Visit 5 [Day 1] to Visit 11 [Week 16]), there is no requirement for eculizumab to be administered on the day of a study visit. Details regarding eculizumab dosing requirements during the study can be found in Section 13 of the protocol.

O. Return of investigational product only to be completed at Week 54 during the Follow-up Period.

P. If a subject's screening visit is completed greater than 28 days prior to dosing, a screening hematology panel should be **repeated** within 28 days of dosing to confirm patient eligibility [Inclusion Criteria 4, 5, 6, and 7].

Q. Transfusion history from the previous 12 months should be collected at the Visit 1 Screening Visit. At Visit 2, transfusion history should be reviewed, and any transfusions received between Visit 1 and Visit 2 should be recorded.

R. During the Screening Period (from up to Week -12 to Week -4 (day -28)), clinical laboratory tests (e.g. hematology, coagulation, serum chemistry, flow cytometry, urinalysis) may be repeated with written approval from the Sponsor (including the assigned Medical Monitor), with no requirement to designate the subject as a screen failure. Subjects that do not meet clinical laboratory-related screening criteria may still qualify for study entry without having to complete the full rescreening process as long as all clinical laboratory-related values meet the criteria for study entry within the Screening Period.

CCI [redacted]

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CCI [redacted]

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CCI [redacted]

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17.3 Sensitivity Analyses for the 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 Hb level at Week 16 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 Eculizumab group will rely on the MAR assumption. Imputation of the primary outcome values in the APL-2 group will be done as if the subject had been on Eculizumab. Imputed values in the APL-2 group will be sampled using the imputation model of the Eculizumab group, i.e., conditional on the outcome values observed at the time points prior to discontinuation. This approach does not assume a sustained benefit of APL-2 after discontinuation but rather assumes a post-discontinuation effect like that of Eculizumab and time effects based the estimated correlations among the time points in the Eculizumab arm. 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 Hb level and Hb 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 Eculizumab 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 APL-2 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 Hb level at Week 16 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 APL-2 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).