Apellis

Protocol No: APL2-302

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)

PEGASUS

Phase: 3

Version: Amendment 4; Version 1.0

Date: 16 August 2019

EudraCT No.: 2017-004268-36

INVESTIGATOR AGREEMENT

Long Title:	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)
Short Title:	PEGASUS
Protocol Number, Version and Date:	APL2-302/ Amendment 4; Version 1.0/ 16 August 2019
Study Phase:	Phase 3
Sponsor Name and Address:	Apellis Pharmaceuticals, Inc. 6400 Westwind Way, Suite A Crestwood, KY 40014 USA
Investigational Test Article:	APL-2
US IND Number:	123087
EudraCT Number:	2017-004268-36
Indication Studied:	PNH
Investigator Agreement:	I have read the clinical study described herein, recognize its confidentiality, and agree to conduct the described trial in compliance with Good Clinical Practices (GCP), the ethical principles contained within the Declaration of Helsinki, this protocol, and all applicable regulatory requirements.
Principal Investigator:	Name: _____ Signature: _____ Date: _____/_____/_____ (DD/MMM/YYYY)

AMENDMENT 4: SUMMARY OF CHANGES FROM THE PREVIOUS VERSION

The primary purpose of APL2-302 Amendment 4 is to alter the criteria for dose adjustment in the study. Based on review of emerging data regarding acute hemolysis, Apellis has decided to revise section 12.2.3.1 of the protocol to mandate dose escalation after a single measurement of LDH that is >2x the upper limit of normal (ULN), rather than requiring 2 consecutive measurements 1 week apart while allowing the investigator to consider whether the dose should be escalated.

This action is being taken to reduce the risk of breakthrough hemolysis that could occur from delaying the dose increase, in the event that a subject experiences LDH elevated above 2x ULN.

In addition: vaccination, transfusion history, and screening period laboratory assessment requirements have been clarified as described in the table below. These were previously addressed in clarification memos and are incorporated into this protocol amendment.

Protocol Versions		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment 4 **Version 1.0**	**Amendment Date** **16 August 2019**	**Global**
Description of Change		**Section(s) Affected by Change**
Streptococcus pneumoniae vaccination requirement scenarios have been clarified as follows: 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 during the run-in period, a dose of PCV13 will be administered at least two weeks prior to Day 1 and a dose of PPSV23 will be administered at least 8 weeks later.~~ If not previously documented, patients will also be vaccinated against *Haemophilus influenzae* Type B (Hib). Vaccination is mandatory unless documented evidence exists that subjects are non-responders to vaccination as evidenced by titers or display titer levels within acceptable local limits. The PI will discuss with the Sponsor in regard to individual patient circumstances. *Streptococcus pneumoniae* vaccination requirement scenarios are as follows (unless documented evidence exists that subjects are non-responders to vaccination as evidenced by titers or display titer levels within acceptable local limits): • If, within 2 years prior to initiating treatment with APL-2, the subject has documented *Streptococcus pneumoniae* vaccination with both the PCV13 vaccine and the PPSV23 vaccine, no additional *Streptococcus pneumoniae* vaccination is required for study entry.		Section 4 Schedule of Events Section 13.2.1 Vaccinations

• If, within 2 years prior to initiating treatment with APL-2, the subject has no documented *Streptococcus pneumoniae* vaccination with either the PCV13 vaccine or the PPSV23 vaccine, then the subject *must* receive the PCV13 vaccine within 2 weeks of Day 1, followed by the PPSV23 vaccine after at least 8 weeks, as indicated in the protocol. • If, within 2 years prior to initiating treatment with APL-2, the subject has documented *Streptococcus pneumoniae* vaccination with the PCV13 vaccine only, then the subject *must* receive the PPSV23 vaccine within 2 weeks prior to Day 1, followed by a PPSV23 booster vaccine at least 8 weeks later. • If, within 2 years prior to initiating treatment with APL-2, the subject has documented *Streptococcus pneumoniae* vaccination with the PPSV23 vaccine *only*, then the subject *must* receive the PPSV23 booster vaccine within 2 weeks prior to Day 1.	
Pre-randomization transfusion history collection requirements have been clarified in Footnote Q in the Schedule of events as follows: 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.	Section 4 Schedule of Events
Screening period laboratory assessment qualification requirements have been clarified as follows: R. During the Screening Period (from up to Week -12 to Week -4), 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.	Section 4 Schedule of Events Section 13.1 Screening (Week -4 up to Week -12)
Section 12.2.3.1 APL-2 Dose Adjustment has been updated as follows to mandate dose escalation upon the first instance of subject reporting of LDH >2xULN as follows: Following commencement of monotherapy with APL-2, i.e., at Day 1 (randomization) or at Week 21, LDH will be monitored as part of the scheduled assessments at the planned clinic visits. For subjects receiving APL-2	Section 12.2.3.1

monotherapy, if LDH is >2 x ULN ~~on 2 consecutive occasions, at least one week apart,~~ an APL-2 dose increase to 1,080 mg every third day should be initiated ~~considered~~ (see Section 8.2). Any adjustment in dose must be ~~will be discussed and confirmed~~ documented in writing to ~~by~~ Apellis. In the event of a dose increase LDH will be monitored bi-weekly (unscheduled assessments if applicable) for at least four weeks to assess the impact of the dose adjustment on LDH levels.	

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Sponsor	Apellis Pharmaceuticals, Inc. 6400 Westwind Way, Suite A Crestwood, KY 40014 USA
Sponsor Representative	PPD Chief Medical Officer PPD PPD

2. ABBREVIATIONS

ADA	Anti-drug Antibodies
ADL	Activities of daily living
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AP50	Alternative Pathway
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
B-HCG	Beta-human Chorionic Gonadotropin
BID	Twice Daily
biw	Twice weekly
BUN	Blood urea nitrogen
°C	Degrees Celsius
C3	Complement Component 3
CABG	Coronary artery bypass grafting
CD71+	Transferrin Receptor
CH50	Total hemolytic complement activity assay
CK	Creatine kinase
cm	Centimeter(s)
CRF	Case report form
CS	Clinically significant
dL	Deciliter
DSMB	Data safety monitoring board
ECG	Electrocardiogram
eCRF	Electronic case report form
EORTC	European Organisation for Research and Treatment of Cancer
EPO	Erythropoietin
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	United States Food and Drug Administration

G	Gram(s)
GCP	Good clinical practice
GGT	Gamma-glutamyl transpeptidase
GLP	Good laboratory practice
µg	Microgram(s)
Hb	Hemoglobin
hERG	Human ether-à-go-go-related gene
Hib	Haemophilus influenzae Type B (vaccine)
HV	Healthy Volunteer
IB	Investigator's brochure
ICH	International Conference on Harmonization
ICD	Implantable Cardiac Defibrillator
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IEC	Institutional Ethics Committee
IND	Investigative New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IV	Intravenous
IVT	Intravitreal
kDa	Kilodalton
kg	Kilogram(s)
L	Liter(s)
LASA	Linear Analog Assessment Scale
LDH	Lactate dehydrogenase
LTSE	Long term safety extension
MAC	Membrane attack complex
MAR	Missing at random
MedDRA®	Medical Dictionary for Regulatory Activities
Mg	Milligram(s)

Min	Minute(s)
mL	Milliliter(s)
ms	Milisecond(s)
NCS	Not clinically significant
NOAEL	No observed adverse effect level
NIM	Non-inferiority margin
NOEL	No observed effect level
NYHA	New York Heart Association
NZW	New Zealand White
PCV13	Pneumococcal conjugate vaccine
PD	Pharmacodynamic(s)
PEG	Polyethylene glycol
PEG40	Polyethylene glycol (40 kDa nominal molecular weight)
PI	Principal Investigator or designee
PK	Pharmacokinetic(s)
PP	Per-protocol
PPSV23	Pneumococcal polysaccharide vaccine 23
PRBC	Packed red blood cell
RBC	Red blood cell
SC	Subcutaneous
TEAE	Treatment emergent adverse event
ULN	Upper Limit of Normal
USA	United States of America
WBC	White blood cell

3. SYNOPSIS

Protocol Number:

APL2-302

Protocol Title:

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)

Version Number:

Amendment 4; Version 1.0

Investigational Product, Dose and Route of Administration:

- APL-2
- 1,080 mg twice weekly
  - Dose adjustment to 1,080mg every 3 days, if required
- Subcutaneous infusion

Study Phase and Type:

Phase 3, randomized, multi-center, open-label, active-comparator controlled study

Number of Planned Subjects:

Sufficient patients to have 70 randomized to the two treatment groups: 35 patients to the APL-2 group and 35 patients to the eculizumab group

Treatment Groups:

- Group 1: APL-2
- Group 2: Eculizumab

Duration of Study Participation:

The planned length of participation in the study for each subject is a maximum of approximately 72 weeks, including a 8-week screening period, 52-week treatment period and 12-week follow-up period. Subjects will be offered entry into an open-label extension study at the end of the 52-week treatment period; those who enter the open label extension study will not require the 12-week follow-up period.

The 52-week treatment period will include a 4-week run-in period (Day -28 to Day -1, where Day -28 is the first day of APL-2 dosing) followed by a 16-week Randomized Controlled Period (Day 1 to Week 16, where Day 1 is the day of randomization) and then a 32-week Open-Label APL-2 Period (Week 17 to Week 48).

Study Population:

Patients, at least 18 years of age, with paroxysmal nocturnal hemoglobinuria (PNH) who are receiving eculizumab therapy, but continue to have Hb levels <10.5 g/dL.

Rationale for the Study:

Phase 1 clinical experience has demonstrated that APL-2 provides sustained inhibition of hemolytic activity in PNH patients who have never received eculizumab (Protocol APL2-CP-PNH-204, New Zealand) and in patients receiving eculizumab (Protocol APL-CP0514, US) who continue to be anemic (Hb <10.5 g/dL). To date, no safety signals have emerged from on-going studies in PNH patients that preclude further development. Thus, this proposed Phase 3 study's aim is to confirm treatment efficacy and safety of APL-2 monotherapy for the treatment of PNH.

Study Objectives and Endpoints:

Objectives

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

Endpoints

Primary Efficacy Endpoint:

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

Key Secondary Efficacy Endpoints:

- Transfusion avoidance (Yes/No), defined as the proportion of patients who do not require a transfusion during the study during the Randomized Controlled Period
- Change form 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

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

Pharmacokinetic Endpoint:

- APL-2 pharmacokinetic concentrations

Pharmacodynamic Endpoints:

- Change from Baseline to Week 16 and Week 48 in percentage 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

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

Safety summaries will be presented over the run-in period, 16 weeks of randomized treatment and 32 weeks of open-label treatment, as well as the overall duration of the study.

Study Design:

This is a prospective, randomized, multi-center, open-label, active-comparator controlled study. A total of approximately 70 PNH patients who are receiving eculizumab and meet all the

inclusion criteria and none of the exclusion criteria will be randomized to receive either APL-2 or eculizumab. The treatment period of the study will consist of three parts: a 4-week run-in period, a 16-week Randomized Controlled Period and a 32-week open-label APL-2 only period.

During the 4-week run-in period (Week -4 to Day -1) all subjects will receive self-administered twice-weekly subcutaneous 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 schedule. 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.

The randomization will be stratified by the following values:

- 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)

The sample size is planned to include approximately 50% of the subjects in each strata (PRBC transfusions <4, PRBC transfusions ≥4). Enrollment of subjects with <4 transfusions will be limited to ≤50%. To obtain adequate control of the allocation of subjects between strata, the randomization will be done centrally.

Day 1 to Week 16 is defined as the Randomized Controlled Period, over which endpoints are assessed.

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 during 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 end of the trial is defined as when the last subject either completes their Week 48 visit and enrolls in the long-term safety extension (LTSE) study, or, should a subject elect not to enter the LTSE study, when the last subject completes their exit visit at Week 60.

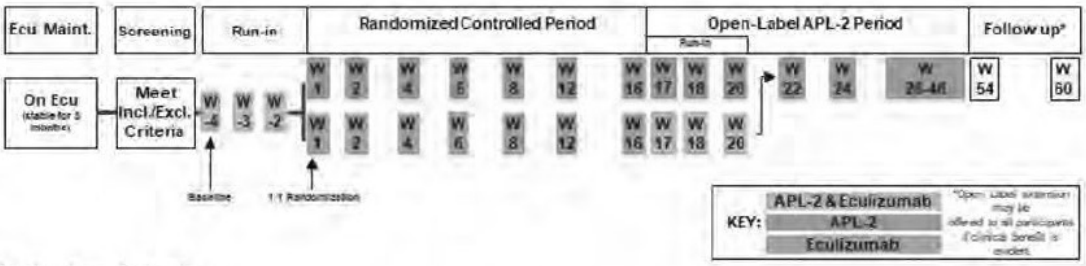
Subjects who withdraw from treatment prior to the Week 48 visit will be encouraged to continue their participation in the study and return to the study site for their scheduled study procedures, with the exception of APL-2 administration. Subjects who withdraw from the study prior to Week

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

An external, independent Data and Safety Monitoring Board (DSMB) will assess the progress and cumulative safety/tolerability data of the study.

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.

STUDY OUTLINE



Inclusion Criteria:

- At least 18 years of age
- Primary diagnosis of PNH confirmed by high-sensitivity flow cytometry
- On treatment with eculizumab. Dose of eculizumab must have been stable for at least 3 months prior to the Screening Visit
- Hb <10.5 g/dL at the Screening Visit
- Absolute reticulocyte count >1.0 x ULN at the Screening Visit
- Platelet count of >50,000/mm^3 at the Screening Visit
- Absolute neutrophil count >500/mm^3 at the Screening Visit
- Vaccination against *Neisseria meningitidis* types A, C, W, Y and B, *Streptococcus pneumoniae* and *Haemophilus influenzae* Type B (Hib) either within 2 years prior to Day 1 dosing, or within 14 days after starting treatment with APL-2. Unless documented evidence exists that subjects are non-responders to vaccination as evidenced by titers or display titer levels within acceptable local limits
- Women of child-bearing potential (WOCBP) must have a negative pregnancy test at the Screening and Day -28 Visit (Run-in Period) and must agree to use protocol defined methods of contraception for the duration of the study and 90 days after their last dose of study drug
- Males must agree to use protocol defined methods of contraception and agree to refrain from donating sperm for the duration of the study and 90 days after their last dose of study drug
- Willing and able to give informed consent
- Willing and able to self-administer APL-2 (administration by caregiver will be allowed)
- Have a body mass index (BMI) <35.0 kg/m^2

Exclusion Criteria:

1. Active bacterial infection that has not resolved within 1 week of Day -28 (first dose of APL-2)
2. Receiving iron, folic acid, vitamin B12 and EPO, unless the dose is stable, in the 4 weeks prior to Screening
3. Hereditary complement deficiency
4. History of bone marrow transplantation
5. History or presence of hypersensitivity or idiosyncratic reaction to compounds related to the investigational product or SC administration
6. Participation in any other investigational drug trial or exposure to other investigational agent within 30 days or 5 half-lives (whichever is longer)
7. Currently breast-feeding women
8. Inability to cooperate or any condition that, in the opinion of the investigator, could increase the subject's risk of participating in the study or confound the outcome of the study

This study includes cardiac safety evaluations. The following cardiac eligibility criteria are necessary to avoid confounding the cardiac safety outcomes:

9. History or family history of Long QT Syndrome or torsade de pointes, unexplained syncope, syncope from an uncorrected cardiac etiology, or family history of sudden death
10. Myocardial infarction, CABG, coronary or cerebral artery stenting and /or angioplasty, stroke, cardiac surgery, or hospitalization for congestive heart failure within 3 months or greater than Class 2 Angina Pectoris or NYHA Heart Failure Class >2
11. QTcF >470 ms, PR >280 ms
12. Mobitz II 2nd degree AV Block, 2:1 AV Block, High Grade AV Block, or Complete Heart Block unless the patient has an implanted pacemaker or implantable cardiac defibrillator (ICD) with backup pacing capabilities
13. Receiving Class 1 or Class 3 antiarrhythmic agents, or arsenic, methadone, ondansetron or pentamidine at screening
14. Receiving any other QTc-prolonging drugs (see Appendix 4 in Section 19.4), at a stable dose for less than 3 weeks prior to dosing
15. Receiving prophylactic ciprofloxacin, erythromycin or azithromycin for less than one week prior to the first dose of study medication (must have a repeat screening ECG after one week of prophylactic antibiotics with QTcF <470 ms)

Sample Size:

A sample size of 64 randomized subjects (32 in each group) provides 90% power (using a 2-sided test at the 5% level of significance) of obtaining a statistically significant difference between the treatment groups in the primary endpoint, Week 16 change from baseline in hemoglobin level. This assumes a treatment difference of 1 g/dL and a standard deviation for the change from baseline of 1.2 g/dL. 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 1.4 g/dL the power is reduced to 80%. Consequently a blinded sample size re-assessment may be performed prior to the completion of study enrollment. 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.

Statistical Methods:

Efficacy: all efficacy analyses will be analyzed with the intent to treat (ITT) Set, defined as those subjects randomized to study treatment on Day 1.

Baseline for efficacy endpoints will be taken as the average of measurements prior to APL-2 dosing on Day -28. To preserve the Type 1 error a fixed sequence testing strategy will be used. All tests will be performed at the 0.05 level following the pre-specified order. The key secondary and 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.

Primary Efficacy Analyses

The primary efficacy endpoint is the change from Baseline to Week 16 in the Hb level. For the primary analysis, missing Hb levels will be imputed using the technique of multiple imputations, under the assumption that Hb levels are missing at random (MAR). If a subject receives a transfusion during their treatment period the pre-transfusion Hb value (central or local laboratory reading) will be used in the calculation of the primary endpoint as their Week 16 value.

For each imputed dataset, the Week 16 change from baseline will be calculated and then analyzed using analysis of covariance (ANCOVA). Stratification variables will be included as covariates. Baseline Hb will be included as a continuous covariate. Combining the results from these individual analyses the difference between treatment groups will be estimated, along with its 95% confidence interval and p-value.

Key Secondary Efficacy Analyses

1) The proportion of patients with transfusion avoidance will be provided for both treatment groups. Also, the difference in the proportion of patients with TA between APL-2 and eculizumab and its 95% CI will be calculated. If the lower bound of the 95% CI for the difference in the proportion of patients with TA between APL-2 and eculizumab is greater than the non-inferiority margin of -20%, then APL-2 will be considered to be non-inferior to eculizumab and the next endpoint will be tested.

2) The change from Baseline to Week 16 in reticulocyte count will be analyzed using the same method as the primary efficacy endpoint. If the upper bound of the 95% CI for the difference between APL-2 and eculizumab treatment groups in the change from baseline in reticulocyte count is less than the non-inferiority margin of 10 (10^9/L), then APL-2 will be considered to be non-inferior to eculizumab and the next endpoint will be tested.

3) The change from Baseline to Week 16 in LDH will be analyzed using the same method as the primary efficacy endpoint. If the upper bound of the 95% CI for the difference between APL-2 and eculizumab treatment groups in the change from baseline in LDH is less than the non-inferiority margin of 20 (U/L), then APL-2 will be considered to be non-inferior to eculizumab and the next endpoint will be tested.

4) The change from Baseline to Week 16 in FACIT-fatigue score will be analyzed using the same method as the primary efficacy endpoint. If the lower bound of the 95% CI for the difference between APL-2 and eculizumab treatment groups in the change from baseline in FACIT-fatigue score is greater than the non-inferiority margin of -3, then APL-2 will be considered to be non-inferior to eculizumab and the next endpoint will be tested.

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.

Secondary Efficacy Analyses

- Superiority will be assessed for the change from Baseline to Week 16 in LDH
- For binary response endpoints, the number and percentage of subjects who respond 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 & Nurminen method. Subjects who receive a transfusion prior to Week 16 will be analyzed as non-responders. As missing data may potentially bias the outcome of the statistical analyses and the subsequent estimation of the magnitude of the treatment effect, different strategies including various sensitivity analyses will be applied to provide a balanced assessment of treatment efficacy.
- Continuous endpoints will be analyzed using the same model as the primary efficacy endpoint.

Safety

All safety analyses will be summarized for the Safety Set.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) AE dictionary. All AEs, including TEAEs, will be summarized by system organ class, preferred term, treatment group for number of subjects and proportion reporting the event. A similar summary will be produced for prior to treatment AEs, SAEs, AEs leading to termination, severe AEs, and AEs related to the investigational product. The intensity of AEs and the relationship to investigational product will be summarized for each system organ class and preferred term by treatment group. Withdrawals due to AEs will be summarized for each body system and preferred term by treatment group.

Clinical laboratory assessments, vital signs and ECGs will be summarized by treatment group using appropriate descriptive statistics.

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 and the database has been cleaned for all visits up to and including Week 16.

A blinded sample size re-assessment may be performed prior to the completion of study enrollment.

4. SCHEDULE OF EVENTS

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]						
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

Protocol: APL2-302

Amendment 4; Version 1.0: 16-AUG-2019

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
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
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		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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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
Questionnaire																		
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 *Haemophilus 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 for 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. 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] 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.

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), 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.

5. INTRODUCTION

5.1 Background

This study is being conducted as part of a series of studies for the clinical development of APL-2. The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements. The subject population will be comprised of adult male and female subjects with paroxysmal nocturnal hemoglobinuria (PNH).

5.1.1 Paroxysmal Nocturnal Hemoglobinuria

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

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

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

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

5.1.2 APL-2

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

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

APL-2 injection (drug product) is a solution of APL-2 in 5% dextrose or a solution of APL-2 in acetate-buffered mannitol or a solution of APL-2 in acetate-buffered sorbitol for SC administration. APL-2 is being developed for the treatment of paroxysmal nocturnal hemoglobinuria (PNH).

Further details can be found in the APL-2 Investigator's Brochure (Apellis Pharmaceuticals, June 2017).

5.1.3 Rationale for Treatment with APL-2

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

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

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

6. NON-CLINICAL DATA

Further details can be found in the APL-2 Investigator's Brochure.

6.1 Pharmacology

Primary Pharmacology: Subcutaneous (SC) and intravenous (IV) doses of APL-2 were shown to be pharmacologically active (as measured by a drop in CH50) in monkeys as soon as 8 hours following initial administration and persisting up to 72 hours after the last dose. *Ex vivo* studies conducted with blood from PNH patients revealed that an APL-2 concentration of ≥100 µg/mL can protect PNH erythrocytes (RBCs) from complement-mediated lysis while simultaneously preventing RBC opsonization by C3 fragments. APL-2 was as effective as eculizumab, an anti-C5 monoclonal antibody approved for PNH, in protecting PNH erythrocytes against membrane attack complex-mediated hemolysis but, unlike eculizumab, APL-2 was also effective in preventing opsonization of those cells by C3 fragments.

6.2 Safety Pharmacology

The potential for APL-2 to inhibit human ether-a-go-go gene- (hERG-) encoded ion channels and pose a risk for cardiac arrhythmias indicates that such a risk is low. Similarly, no evidence of APL-2-related adverse effects on myocardial conduction, cardiovascular and respiratory systems, and body temperature control mechanisms have been observed in either Pharmacokinetics.

Pharmacokinetic (PK) and toxicokinetic (TK) assessments of APL-2 have been investigated after IV and SC administration to New Zealand White (NZW) rabbits and cynomolgus monkeys. The PK behavior of APL-2 in rabbits and monkeys has been consistent with the expected PK behavior of a PEGylated peptide. APL-2 is readily absorbed from SC injections in both species, with an estimated bioavailability of approximately 85% in monkeys. Repeated administrations of APL-2 have indicated that absorption is non-linear at higher doses, and the potential for bioaccumulation exists. No gender-related differences have been observed in either species after 6 or 9 months of SC dosing in rabbits and monkeys, respectively. Terminal elimination half-lives ($t_{1/2}$), estimated during 4-week, drug-free, recovery phases of the 28-day SC studies were between 2.48–2.78 days in rabbits and 6.29–8.25 days in monkeys. Similarly, the $t_{1/2}$ was estimated to be between 2.3 and 2.6 days in rabbits and 6.0 days in monkeys after two IV doses separated by 14 days.

6.3 Toxicology

The toxicological potential of APL-2 has been investigated in repeat-dose toxicity studies in rabbits and monkeys across three routes of administration (SC, IV, IVT) under a testing strategy designed to facilitate differentiation between potential changes attributable to APL-2, per se, and those attributable to the PEG40 domain of the drug molecule.

Daily subcutaneous administration of APL-2 and PEG40 for a duration of 6 months in rabbits and 9 months in monkey were associated with little systemic toxicity noted in either species beyond observations in the kidney (noted below). APL-2 and PEG40 were weakly to mildly immunogenic in rabbits, but not significantly immunogenic in monkeys. Single- or multi-tissue (or multi-organ) macrophage vacuolation was consistently observed in both species, and

generally comparable in incidence and severity between APL-2- and PEG40-treated groups; thus, it was concluded the finding were caused by the PEG40 domain present within APL-2. Renal tubular degeneration was observed with a higher incidence in the monkey 9-month study in APL-2-treated animals compared to the PEG40-treated ones and was concluded to be APL-2 related.

The no-observed-adverse-effect-level (NOAEL) for SC-administered APL-2 was <1 mg/kg/d in rabbits and approximately 7 mg/kg/d in monkeys after 6- and 9-month chronic dosing, respectively.

Intravenous arms included in the 28-day repeat-dose SC studies of APL-2 in rabbits and monkeys suggested that IV-administered APL-2 was well-tolerated in both species, with only vacuolation of tubular epithelial cells in the kidney observed microscopically in rabbits (which, again, was deemed to be caused in part by the PEG40 domain of APL-2). IV APL-2 was mildly immunogenic in rabbits (albeit less than what was observed by the SC route), and without immunologic effects in monkeys. The no-observed--effect-level (NOEL) by the IV route of administration for both rabbits and monkeys was determined to be ≥42 mg/kg after two doses separated by 14 days.

Repeated intravitreal administration (i.e., once every 4 weeks) of APL-2 to monkeys for up to 9 months was well-tolerated and revealed no drug-related systemic or ophthalmological changes. APL-2 may be minimally immunogenic when administered intravitreally, as evidenced by a single monkey having a marginal titer of APL-2 antibodies. The NOEL by the IVT route of administration for monkeys was determined to be ≥24.8 mg/eye.

APL-2 has not demonstrated genotoxic potential in any *in vitro* or *in vivo* genotoxicity assays conducted, to date.

7. CLINICAL DATA

To date, two Phase 1 studies in healthy volunteers have been conducted to assess safety and PK parameters of APL-2 administered as single and multiple dose SC injections and to guide dose selection for clinical studies in PNH subjects.

A single Phase 1 single ascending dose has evaluated intravenous (IV) dosing of APL-2 in healthy volunteers.

A further five Phase 1 studies evaluating APL-2 delivered by SC injection are either planned or ongoing. These include two studies in healthy volunteers, a study in subjects with severe renal impairment and two ongoing clinical studies in PNH patients.

A Phase 2 study in patients with autoimmune hemolytic anemia is also ongoing.

7.1 Completed Clinical Studies in Healthy Volunteers

The two completed clinical studies investigating the safety, tolerability and PK of single (APL-CP-0713-1) and multiple (APL-CP-1014) SC doses of APL-2 in healthy volunteers showed that overall, single doses of APL-2, up to a dose of 1440 mg, and repeated daily doses of APL-2 up to a dose of 270 mg, appeared safe and well tolerated when administered to healthy volunteers by SC injection.

Serum APL-2 concentrations generally increased linearly with dose. APL-2 was slowly absorbed into the systemic circulation with median T_{max} values between 4.5 and 6 days across the dose groups. APL-2 serum concentration declined in a steady mono-exponential manner with a consistent rate of decay across two studies for all dose groups. Both studies demonstrated a slow terminal elimination with median t½ values between 8 and 10 days.

Plasma complement C3 increased with increasing dose and a general dose-dependent reduction in AP50 was observed following multiple dosing with APL-2. Pharmacodynamic (PD) observations were consistent with a conclusion that APL-2 interacts with complement C3 and inhibits its activation.

Further details can be found in the current APL-2 Investigator's Brochure.

7.2 Ongoing Clinical Studies

As of 01 January 2018, there are two ongoing Phase 1 clinical studies evaluating SC administered APL-2 in PNH patients (APL-CP0514 and APL-2-CP-PNH). An interim analysis has been performed for both studies with a data cut at 85 days of treatment for all subjects.

- APL-CP0514 is a Phase 1b, open-label study being conducted at multiple clinical sites in the United States to assess the safety, tolerability, PK and PD of APL-2 as an add-on to eculizumab in subjects with PNH. The study is comprised of 4 cohorts in total; 3 cohorts (Cohorts 1-3) with two subjects per cohort, and one cohort with six subjects (Cohort 4). Cohorts 1 to 3 have completed and Cohort 4 is ongoing. All six subjects in Cohort 4 completed at least 3 months of treatment with APL-2 270 mg/d. Based on the clinical benefit observed, the clinical protocol was amended to allow subjects to continue to receive dosing with APL-2 for up to 2 years. As of 01 January 2018, 4 of the 6 subjects in Cohort 4 are ongoing and continue to receive APL-2 at a dose of 270 mg/day and 2 subjects have

withdrawn from the study; 1 subject became pregnant and was withdrawn as per protocol and the 2nd subject was withdrawn following a number of adverse events related to other co-morbidities. Subjects who continue to receive dosing with APL-2 have maintained hemoglobin levels without the need for transfusion and other markers of hemolytic activity demonstrating ongoing control of hemolysis.

- APL-2-CP-PNH-204 is a Phase 1b, open-label study in patients with PNH who have never received treatment with eculizumab. The study initially comprised of 2 cohorts with three subjects in Cohort 1 (180 mg/day APL-2) and at least 6 subjects in Cohort 2 (270 mg/day APL-2). Cohort 1 has completed and Cohort 2 is ongoing. The study was expanded to include clinical sites in South East Asia and the USA, and as a result, the number of subjects in Cohort 2 increased with up to 20 subjects in total now planned for enrollment during 2018. The formal interim analysis performed in January 2017 included all subjects ongoing in the study at that time (3 in Cohort 1 and 3 in Cohort 2.) Two of the three subjects who initially entered into Cohort 2 completed 3 months of treatment with APL-2 270 mg/day. The third subject withdrew, for personal reasons, after receiving 29 days of treatment. Based on the clinical benefit observed, both remaining subjects entered an Extension phase allowing them to continue to receive dosing with APL-2 for up to 1 year. One subject received daily doses of APL-2 for >8 months including doses of 360 mg for >3 months, but was diagnosed with a malignancy, unrelated to the study drug, and treatment was withdrawn in April 2017; and the remaining subject continued to receive APL-2 270 mg/day until he presented with thrombocytopenia in October 2017 with a subsequent diagnosis of aplastic anemia. The subject was withdrawn from the study and treatment with APL-2 was discontinued as of 30 November 2017.

Throughout 2018, subjects in South East Asia will be screened and enrolled into the study.

Across the two ongoing studies in PNH patients, a total of 14 subjects with PNH have been dosed with APL-2, with 9 having received 270 mg/day for 28 days and 8 having received ≥270 mg/day for >6 months including 2 subjects who have received 360 mg/day for 2 months. As of 01 January 2018, 4 subjects continue to receive treatment of APL-2 270 mg/day. APL-2 has been generally well tolerated in these subjects. At approximately quarterly intervals, all safety data from both studies, ongoing in PNH patients, is reviewed by members of an independent Safety Monitoring Committee (SMC) who are responsible for providing recommendations with respect to monitoring and continuation of the studies.

As of 01 January 2018, there have been a total of 18 serious adverse events (SAEs) reported in 6 of 14 subjects across the two PNH studies (APL2-CP-PNH-204 and APL-CP0514). Of these, 15 were considered unrelated/unlikely related to APL-2 and 3 have been assigned a causality of possibly related to APL-2 by the Sponsor. Those that were considered possibly related include 1 incidence of hypersensitivity reaction (APL2-CP-PNH-204) and 2 incidences of increased alanine aminotransferase (ALT) (APL-CP0514) in a single subject with a history of hepatobiliary disease and similar ALT increases prior to study entry.

In addition to the SAEs, there have been a total of 11 treatment-emergent adverse events (TEAEs) reported in 2 subjects (one subject was enrolled in two cohorts and received two different subject numbers) that were considered probably related to APL-2 by Investigators. These TEAEs include injection site reaction (n=10) and urinary tract infection (n=1). All TEAEs

that were considered probably related were resolved within one week of their onset. Overall, SC administration of APL-2 in PNH subjects in the two ongoing clinical studies has been generally safe and well tolerated.

8. RATIONALE

Phase 1b clinical experience has demonstrated that APL-2 provides sustained inhibition of hemolytic activity in PNH patients who have never received eculizumab (Protocol APL2-CP-PNH-204, New Zealand) and in PNH patients receiving eculizumab (Protocol APL-CP0514, US) who continue to be anemic (Hb <10.5 g/dL). To date, no safety signals have emerged from ongoing studies in PNH patients that preclude further development. Thus, this proposed Phase 3 study is to further evaluate treatment efficacy and safety of APL-2 as monotherapy in patients with PNH.

8.1 Purpose of the Study

The purpose of this study is to establish the efficacy and safety of APL-2 compared to eculizumab in patients with PNH who continue to have Hb levels <10.5 g/dL despite treatment with eculizumab.

8.2 Dose Selection

Target Level of APL-2 Serum Concentration

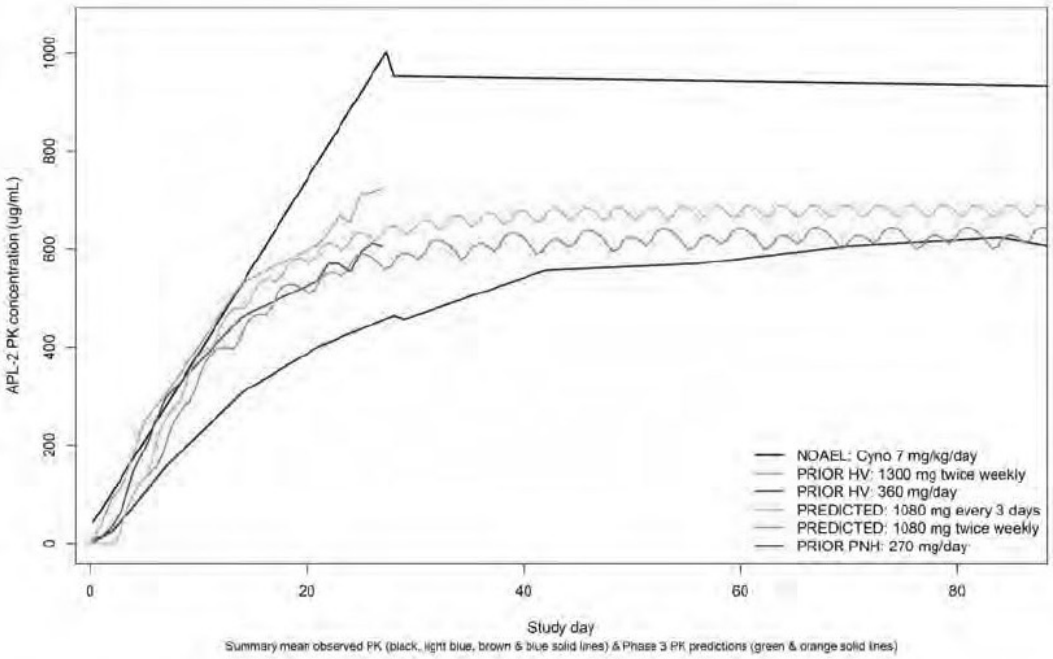
The toxicological data accumulated from the animal studies were used to guide dose selection during the Phase I single ascending dose and multiple ascending dose studies in HVs (protocols APL2-CP-HV-401, APL-CP0713-1 and APL-CP1014 respectively). In particular, the highest doses were selected based on exposure predicted by a PK model and compared with the exposures observed at the no-observed adverse effect level (NOAEL) in cynomolgus monkeys.

The planned dose of APL-2 is 1,080 mg SC twice weekly (equivalent to 308 mg/day). Dose selection is based on past clinical experience with SC APL-2 coupled with nonclinical toxicological studies. Daily doses up to 360 mg/day have been tested in past and ongoing clinical trials and have been found to be well tolerated, with exposures that are well below the APL-2 levels associated with the NOAEL in monkeys. While doses of 180 mg/day and above have been shown to be pharmacologically active in both healthy volunteers and PNH patients, clinical and biomarker responses increased in a dose dependent manner and with the maximum benefits being observed at either doses of 270 or 360 mg/day.

Using a Target Mediated Drug Disposition (TMDD) PKPD model (Mager & Jusko, 2001) the relationship between dosing regimen and APL-2 serum concentration is well understood and well predicted by the model. Presented below in Figure 1 is the predicted PK profile for the planned dose of 1,080 mg twice weekly (green line) compared to the NOAEL PK data observed in the pivotal 9-month chronic toxicological study in monkeys (study 13CATX-004; black line). For comparison with previous human exposure, also included is the summary PK data from the ongoing PNH study APL-CP0514 270 mg/day Cohort (blue line) and healthy volunteer study APL2-101 at 360 mg/day (brown line) and at a higher dose, 1,300 mg twice weekly (light blue line). Both studies demonstrated APL-2 to be safe and well tolerated. The figure illustrates that the PK exposure at the proposed Phase 3 dosing regimen should only derive a small increase in PK exposure previously observed in the PNH study 270 mg/d Cohort (study APL-CP0514), a lower PK exposure (Cmax) than that observed in study APL2-101 (higher dose, 1,300 mg twice

weekly) and should be safely below that observed at the NOAEL. Also included in Figure 1 is the predicted PK level at a dose of 1,080 mg SC every third day, this is discussed below.

Figure 1: Predicted PK profile (green line) at the planned dose of 1,080 mg twice weekly compared to the summary PK data at the NOAEL (13CATX-004; black line), ongoing PNH study APL-CP0514 270 mg/day cohort (blue line) and healthy volunteer study APL2-101 for both the 360 mg/day (brown line) and 1,300 mg twice weekly cohorts (light blue line).



Summary mean observed PK (black, light blue, brown & blue solid lines) & Phase 3 PK predictions (green & orange solid lines)

Dosing Adjustment Option

If a subject does not respond sufficiently to the planned dose of 1,080 mg twice weekly, the dosing regimen may be changed to 1,080 mg every third day upon agreement with the sponsor, equivalent to 360 mg/day. The premise being that to derive a sufficient response in some subjects we may need to target a higher level of APL-2 serum concentrations. The amended dosing regimen will result in a higher PK exposure than that originally planned (twice weekly vs every 3 days). As Illustrated in Figure 1, the increase in PK exposure will be small, continue to be lower (Cmax) than that observed in study APL2-101 (higher dose, 1,300 mg twice weekly) and safely below that observed at the NOAEL.

Details on the criteria to be used to determine whether a subject should receive the dosing amendment is provided in Section 12.2.3.1.

8.3 Risk/Benefit

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

Injection/infusion site and pump use safety will be assessed during clinical visits, and any significant finding from the assessment will be reported as an AE (see Section 14.1.11).

The volume of blood planned for collection from each subject over the course of the study (see Section 14.6) will be minimized in order to limit the impact on the overall health of these anemic subjects.

Systemic complement inhibition might predispose individuals to infections caused by encapsulated organisms, including *Streptococcus pneumoniae, Neisseria meningitidis,* and *Haemophilus influenzae*. At Day -14 all subjects will receive vaccinations, if required (i.e., if not previously vaccinated), against *Streptococcus pneumoniae, Neisseria meningitidis A, C, W, Y and B,* and *Haemophilus influenzae.*

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

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

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

The use of silica reagents in coagulation panels should be avoided. Apellis previously conducted an investigation into prolonged activated partial thromboplastin time (aPTT) observed in subjects treated with APL-2. It was confirmed that false positive aPTT prolongation occurred when coagulation panels were performed using a Stago Analyzer and specifically silica reagents. It was determined that there was interference between the silica reagents and PEGylated APL-2, resulting in artificially prolonged aPTTs.

Details regarding the dosing regimen and administration of APL-2 are provided in Section 12.2. Subjects should be instructed to take their APL-2 treatment as prescribed, and to contact the investigator immediately for guidance in the event of any missed doses. Discontinuation with APL-2 or non-compliance with the prescribed dose regimen may lead to the potential for an

increased risk for serious hemolysis. The Sponsor's medical monitor should be contacted before interrupting or discontinuing treatment with APL-2.

There is an anticipated health benefit for study participants from receipt of study drug. At the proposed dose levels of APL-2, a significant decrease in complement-mediated hemolytic activity was observed in all APL-2-treated subjects (both treatment-naïve and treated previously with eculizumab) in PNH Phase 1b studies and in HV studies. APL-2 is, therefore, expected to reduce complement-mediated hemolytic activity in PNH patients. In this context, a careful evaluation of the risk/benefit ratio should be made. APL-2 at the proposed doses has been deemed safe for up to 9 months of administration in preclinical studies and 28 days in HV studies. In addition, in studies of subjects with PNH (see Section 7.2), ongoing treatment with APL-2 270 mg/d has been well-tolerated and provided clinical benefit to subjects either treated alone or as an add-on to eculizumab.

If efficacious and safe, APL-2 is expected to continue to improve hemoglobin (Hb) levels and reduce transfusion dependency in these patients.

9. STUDY OBJECTIVES AND ENDPOINTS

9.1 Study Objectives

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

9.2 Study Endpoints

9.2.1 Primary Efficacy Endpoint:

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

9.2.2 Key Secondary Efficacy Endpoints:

- Transfusion avoidance (Yes/No), defined as the proportion of patients who do not require a transfusion during the study during the Randomized Controlled Period
- Change form 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

9.2.3 Secondary Efficacy 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

9.2.4 Pharmacokinetic Endpoints:

- APL-2 pharmacokinetic concentrations

9.2.5 Pharmacodynamic Endpoints:

- Change from Baseline to Week 16 and Week 48 in percentage 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

9.2.6 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

10. STUDY DESIGN

This is a prospective, randomized, multi-center, open-label, active-comparator controlled study. A total of approximately 70 PNH patients who are receiving eculizumab and meet all the inclusion criteria and none of the exclusion criteria will be randomized to receive either APL-2 or eculizumab. The treatment period of the study will consist of three parts: a 4-week run-in period, a 16-week Randomized Controlled Period and a 32-week open-label APL-2 only period.

During the 4-week run-in period (Week -4 to Day -1) all subjects will receive self-administered twice-weekly subcutaneous 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 doses 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.

The randomization will be stratified by the following values:

- 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)

The sample size is planned to include approximately 50% of the subjects in each strata (PRBC transfusions <4, PRBC transfusions ≥4). Enrollment of subjects with <4 transfusions will be limited to ≤50%. To obtain adequate control of the allocation of subjects between strata, the randomization will be done centrally.

Day 1 to Week 16 is defined as the Randomized Controlled Period, over which endpoints are assessed.

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 end of the trial is defined as when the last subject either completes their Week 48 visit and enrolls in the long-term safety extension (LTSE) study, or, should a subject elect not to enter the LTSE study, when the last subject completes their exit visit at Week 60.

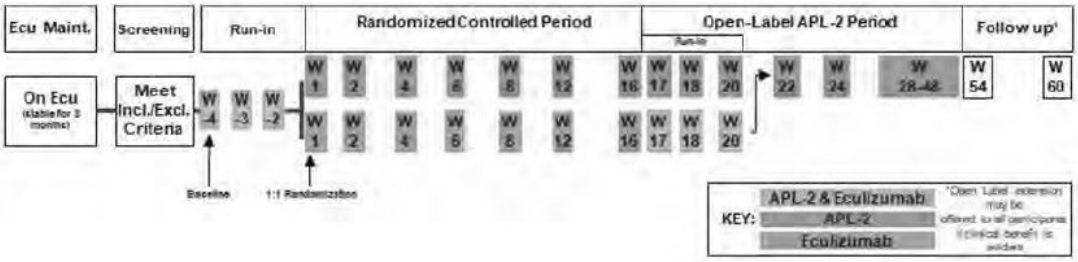
Subjects who withdraw from treatment prior to the Week 48 visit will be encouraged to continue their participation in the study and return to the study site for their scheduled study procedures, with the exception of APL-2 administration. Subjects who withdraw from the study prior to Week 48 and are currently being treated solely with APL-2 are recommended to receive at least one dose of eculizumab before discontinuing APL-2.

An external, independent Data and Safety Monitoring Board (DSMB) will assess the progress and cumulative safety/tolerability data of the study.

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.

STUDY OUTLINE



11. SUBJECT SELECTION

The study is planned to randomize approximately 70 subjects with PNH who are receiving eculizumab therapy, but continue to have Hb levels <10.5g/dL.

11.1 Inclusion Criteria

At Screening (unless otherwise specified), subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. At least 18 years of age.
2. Primary diagnosis of PNH confirmed by high-sensitivity flow cytometry.
3. On treatment with eculizumab. Dose of eculizumab must have been stable for at least 3 months prior to the Screening Visit.
4. Hemoglobin <10.5 g/dL at the Screening Visit.
5. Absolute reticulocyte count >1.0 x ULN at the Screening Visit.
6. Platelet count of >50,000/mm^3 at the Screening Visit.
7. Absolute neutrophil count >500/mm^3 at the Screening Visit.
8. Vaccination against *Neisseria meningitidis* types A, C, W, Y and B, *Streptococcus pneumoniae* and *Haemophilus influenzae* Type B (Hib) either within 2 years prior to Day 1 dosing, or within 14 days after starting treatment with APL-2. Unless documented evidence exists that subjects are non-responders to vaccination as evidenced by titers or display titer levels within acceptable local limits.
9. Women of child-bearing potential (WOCBP) must have a negative pregnancy test at the Screening and Day -28 Visit (Run-in Period) and must agree to use protocol defined methods of contraception for the duration of the study and 90 days after their last dose of study drug.
10. Males must agree to use protocol defined methods of contraception and agree to refrain from donating sperm for the duration of the study and 90 days after their last dose of study drug.
11. Willing and able to give informed consent.
12. Willing and able to self-administer APL-2 (administration by caregiver will be allowed).
13. Have a body mass index (BMI) <35.0 kg/m^2.

11.1.1 Approved Methods of Contraception

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

approved method of contraception during the study and 90 days after their last dose of study drug.

11.2 Exclusion Criteria

Subjects will be excluded from the study if there is evidence of any of the following criteria at screening and confirmed at the Day -28 Visit, as appropriate.

1. Active bacterial infection that has not resolved within 1 week of Day -28 (first dose of APL-2).
2. Receiving iron, folic acid, vitamin B12 and EPO, unless the dose is stable, in the 4 weeks prior to Screening.
3. Hereditary complement deficiency.
4. History of bone marrow transplantation.
5. History or presence of hypersensitivity or idiosyncratic reaction to compounds related to the investigational product of SC administration.
6. Participation in any other investigational drug trial or exposure to other investigational agent within 30 days or 5 half-lives (whichever is longer).
7. Currently breast-feeding women.
8. Inability to cooperate or any condition that, in the opinion of the investigator, could increase the subject's risk of participating in the study or confound the outcome of the study.

This study includes cardiac safety evaluations. The following cardiac eligibility criteria are necessary to avoid confounding the cardiac safety outcomes:

9. History or family history of Long QT Syndrome or torsade de pointes, unexplained syncope, syncope from an uncorrected cardiac etiology, or family history of sudden death.
10. Myocardial infarction, CABG, coronary or cerebral artery stenting and/or angioplasty, stroke, cardiac surgery, or hospitalization for congestive heart failure within 3 months or > Class 2 Angina Pectoris or NYHA Heart Failure Class >2.
11. QTcF >470 ms, PR >280 ms.
12. Mobitz II 2nd degree AV Block, 2:1 AV Block, High Grade AV Block, or Complete Heart Block unless the patient has an implanted pacemaker or implantable cardiac defibrillator (ICD) with backup pacing capabilities.
13. Receiving Class 1 or Class 3 antiarrhythmic agents, or arsenic, methadone, ondansetron or pentamidine at screening.
14. Receiving any other QTc-prolonging drugs (see Appendix 4 in Section 19.4), at a stable dose for less than 3 weeks prior to dosing.

15. Receiving prophylactic ciprofloxacin, erythromycin or azithromycin for less than one week prior to the first dose of study medication (must have a repeat screening ECG after one week of prophylactic antibiotics with QTcF <470 ms).

12. STUDY TREATMENTS

12.1 Identity of Investigational Product

The test product is APL-2, which will be provided as a sterile solution of APL-2, 54 mg/mL, in acetate-buffered sorbitol, supplied in stoppered glass vials. Additional information is provided in the APL-2 Investigator's Brochure.

12.1.1 Blinding the Treatment Assignment

This is a randomized, multi-center, open-label, active-comparator controlled study. Treatment assignment will not be blinded.

12.2 Administration of Investigational Product

12.2.1 Interactive Response Technology (IRT) for Investigational Product Management

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

12.2.2 Allocation to Treatment

This is a randomized, open-label, active-comparator controlled study. Subjects who meet all the inclusion criteria and none of the exclusion criteria will be eligible to enter the 4-week run-in period. During the run-in period, all subjects will receive twice-weekly subcutaneous doses of 1,080 mg of APL-2 in addition to subjects' current dose of eculizumab. Following completion of the run-in period, subjects will be randomly assigned (1:1) to receive either 1,080mg of APL-2 twice-weekly or current dose of eculizumab through the duration of the 16-week Randomized Controlled Period. Following completion of the Randomized Controlled Period, all subjects will be allocated to open-label APL-2 for 32 weeks.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined.

The randomization will be stratified by the following values:

- 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)

The sample size is planned to include approximately 50% of the subjects in each strata (PRBC transfusions <4, PRBC transfusions ≥4). Enrollment of subjects with <4 transfusions will be limited to ≤50%. To obtain adequate control of the allocation of subjects between strata, the randomization will be done centrally.

Individual subject treatment will be automatically assigned by the IRT.

12.2.3 Dosing

Starting on Day -28 (Visit 2), subjects will receive self-administered twice-weekly SC doses of 1,080 mg of APL-2 in addition to their current dose of eculizumab until Day 1. Subjects should maintain their eculizumab dose and administration schedule 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 schedule. Subjects will then be randomized to either Group 1 (monotherapy APL-2) or Group 2 (monotherapy eculizumab).

Subjects in Group 1 will stop their eculizumab treatment and will continue to receive APL-2 (1,080 mg twice a week) on Day 1 and Day 4 of each treatment week until the end of Week 48.

Subjects in Group 2 must continue to receive their pre-screening stable dose of eculizumab until the end of Week 20. Following their Week 16 visit subjects will receive APL-2 (1,080 mg twice a week) on Day 1 and Day 4 of the treatment week until the end of Week 48.

Dosing diaries will be utilized for APL-2 and Eculizumab and are to be completed for each dose administered at the clinic or outside regular clinic visits. Subjects should not deviate from their APL-2 dosing schedule: Day 1 and Day 4 of each treatment week (e.g., Monday/Thursday/Monday) or every 3 days (e.g., Monday/Thursday/Sunday).

Note: Discontinuation with APL-2 or noncompliance with the prescribed dose regimen may lead to the potential for an increased risk for serious hemolysis. Subjects should be instructed to take their APL-2 treatment as prescribed, and to contact the investigator immediately for guidance in the event of any missed doses.

12.2.3.1 APL-2 Dose Adjustments

Following commencement of monotherapy with APL-2, i.e., at Day 1 (randomization) or at Week 21, LDH will be monitored as part of the scheduled assessments at the planned clinic visits. For subjects receiving APL-2 monotherapy, if LDH is >2 x ULN, an APL-2 dose increase to 1,080 mg every third day should be initiated (see Section 8.2). Any adjustment in dose must be documented in writing to Apellis. In the event of a dose increase LDH will be monitored bi-weekly (unscheduled assessments if applicable) for at least four weeks to assess the impact of the dose adjustment on LDH levels.

12.2.4 Investigational Product Administration

Investigational product will be administered as a 20 mL SC infusion.

The preferred site of injection will be the abdomen, however, if a subject does not tolerate administration into the abdomen, alternative appropriate sites may be considered. Research nurses or other appropriately qualified research personnel will administer the SC infusions at the Day -28 Visit (clinic visit) and will supervise the self-administration at a minimum on Day -25 (home or clinic visit), Day -21 (clinic visit) and Day -18 (home or clinic visit) or until the subject has been qualified to conduct self-administration. Following self-administration qualification,

subjects may self-administer the SC infusions without supervision. Once qualified, the patient will continue to self-administer infusions at the clinic on those days when a clinic visit occurs and at an off-site location convenient to the subject on all other days. **Self-administration conducted at the clinic will be supervised to ensure that the subject continues to remain compliant with the administration guidelines.**

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

12.3 Labelling, Packaging, Storage, and Handling

12.3.1 Labelling

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

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

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

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

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

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

12.3.2 Packaging

Investigational product is supplied in 20-cc glass vials.

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

12.3.3 Infusion Supplies

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

12.3.4 Storage

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

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

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

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

12.4 Investigational Product Accountability

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

At the conclusion of the study, any unused investigational product will either be destroyed at the investigator site or be returned to the Sponsor or designee for destruction, and destruction will be documented appropriately. If no supplies remain, this fact will be documented appropriately.

12.5 Subject Compliance

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

12.6 Eculizumab (Active Comparator)

To be eligible for entry into the study subjects will be receiving treatment with eculizumab, with a dose that has been stable for at least 3 months prior to screening. The dose of eculizumab will remain at this stable dose throughout the study except where eculizumab is discontinued on Day 1 for those randomized to APL-2 and at Week 20 for those randomized to Group 2 (monotherapy eculizumab).

Where appropriate, subjects may continue to receive their eculizumab infusion at home, their local infusion center or local hematologist, however, detailed infusion records must be provided and recorded in the CRF. Eculizumab infusion will be administered by caregivers as per standard practice or can be given by research nurses or other appropriately qualified research personnel.

12.7 Concomitant Medications

12.7.1 Transfusions

At the Day -28 Visit, transfusion history from the previous 12 months (including the Screening Period) must be obtained and recorded in the patient CRF. Historical information to be obtained will be:

- Date of transfusion
- Type of infusion (whole blood, PRBCs or other)
- Number of Units transfused
- Pre-transfusion hemoglobin value and associated date of sample (must be within 14 days prior to transfusion)

During the study treatment period (Day -28 to Week 48), transfusions will be administered if Hb is <7 g/dL without symptoms or <9 g/dL with symptoms. The pre-transfusion Hb and number of units transfused must be documented.

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

12.7.2 Prophylactic Antibiotics

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

12.7.3 Rescue Antibiotics

Body temperature, vital signs and relevant blood parameters will be monitored regularly throughout the study to assess for signs of infection. Subjects will be provided with emergency study cards that include a list of symptoms associated with infections. This study card also guides subjects with instructions to contact their study physician or seek emergency medical care in the event they experience any of the listed symptoms. In the event of a suspected infection, the Principal Investigator (PI) should provide guidance on appropriate action to be taken thereafter. Action to be taken may include administration of a broad-spectrum antibiotic.

12.7.4 QT-Prolonging Medication

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

Patients must be on a stable dose of the QT-prolonging medications outlined in Appendix 4 (Section 19.4) for 3 or more weeks prior to dosing (Day -28). Subjects should not be initiated on the medications detailed in Appendix 4 (Section 19.4) during the study unless there is a medical need for the introduction of one of these agents and an alternative, non-QT-prolonging medication is not available. The initiation of any of the medications listed in Appendix 4 (Section 19.4) must be approved by the Sponsor in advance and only if required for patient treatment. All such patients should be carefully monitored for the development of QTc prolongation.

12.7.5 Iron

12.7.5.1 Iron Supplements

For subjects receiving iron supplements at the time of APL-2 initiation, iron supplement doses must be maintained stable throughout the study unless iron levels (ferritin and TIBC) increase above ULN.

12.7.5.2 Iron Chelation

If patients have previously received and tolerated iron chelation this may be continued or re-initiated throughout the study.

12.7.5.3 Phlebotomy/Venesection for Iron Overload

Phlebotomy/Venesection should only be considered if the Hb is with the normal range and may only be initiated if the need and frequency have been discussed and agreed to with the Sponsor.

13. STUDY PROCEDURES

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

Administration of Eculizumab at Study Visits

During the Run-in Period for all subjects (Visit 2 [Week -4] 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. Subjects should adhere to their regular eculizumab administration schedule, and a subject's eculizumab administration schedule should not factor into study visit scheduling. Subjects may receive eculizumab at the site, but there is no requirement to do so even in instances in which the subject's regular eculizumab administration schedule aligns with a study visit day (e.g., even if the subject is to receive eculizumab on the day of a scheduled study visit, the subject may receive eculizumab at an off-site location different than the study site). Through the Run-in Period and at Visit 5 (Day 1) if a subject does not receive eculizumab on the day of a study visit, all visit procedures designated "pre-dose" should be performed on arrival or prior to APL-2 administration. The last dose and time of administration of the subject's previous eculizumab dose should be recorded.

If eculizumab dosing falls on the day of a study visit and the subject is to receive eculizumab at the study site, the site should conduct all "pre-dose" study procedures before the administration of eculizumab. If a subject is randomized to eculizumab for the Randomized Controlled Period and elects to administer eculizumab at the study site at Visit 11 (Week 16), all procedures designated as "post investigational product administration assessments" (post-dose ECG, vital sign measurements, PK sample, and AE collection) should be performed following the administration of eculizumab. If a subject randomized to eculizumab does not elect to administer eculizumab at the study site at Visit 11 (Week 16), the "post investigational product administration assessments" should not be performed.

Administration of APL-2 at Study Visits

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). 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 as outlined in this protocol (Section 13 and the Schedule of Events [Section 4]).

In some instances, however, a subject may not be able to align the date of a study visit with his/her APL-2 administration schedule (e.g., if the subject has to utilize the visit window in order to be able to attend a study visit, or if the subject is switched to a dosing regimen of APL-2 every three days). In such instances it is important that APL-2 dosing occurs according to the dosing schedule and not the visit schedule. There is no requirement for subjects to administer APL-2 at the study site, and the visit should be conducted on a date within the study visit window that the

subject is able to attend. If a subject does not administer APL-2 at the study site on the day of a study visit, the site should conduct all "pre-dose" study procedures as outlined in this protocol (Section 13 and the Schedule of Events [Section 4]) but will not conduct the procedures designated as "post investigational product administration assessments." Procedures not conducted should be designated as "Not Done" on the CRF and the reason provided should be "APL-2 not administered during the clinic visit." Such instances should not be recorded as a protocol deviation.

There are 2 visits for which aligning the date of the study visit with the subject's APL-2 administration schedule in order to facilitate APL-2 administration at the study site should be prioritized: Visit 11 (Week 16) and Visit 22 (Week 48). If necessary, visit windows should be utilized for these visits in order to ensure that the subject is able to administer APL-2 during these visits and complete the "post investigational product administration assessments," as outlined in the protocol. If, however, a subject is unable to align APL-2 administration with either of these study visits, the visit should still be conducted within the visit window and "post investigational product administration assessments" should not be performed and will be recorded on the CRF as noted above.

13.1 Screening (Week -4 up to Week -12)

The subject will be screened to confirm that the subject selection criteria for the study has been met. Informed consent will be obtained at screening prior to any study related procedures being conducted (see Section 17.1.3).

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

Subjects should not be rescreened once they have been designated as a screen failure, unless this is discussed in advance and documented in writing with the sponsor.

During the Screening Period (from up to Week -12 to Week -4), 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.

Confirm sufficient supplementation of iron, folic acid and vitamin B12 prior to treatment phase. If not, subjects need to be treated with supplements for at least 4 weeks prior to Screening. Screening procedures are listed in the Schedule of Events in Section 4.

The following assessments will be performed:

- Informed consent
- Demographics
- Medical history (including thrombosis history)

- Review of inclusion/exclusion criteria
- Physical examination
- Triplicate 12-lead ECG
- Prior and concomitant medications
- Vital sign measurements
- Urinalysis
- Blood tests (see schedule of events for details)
    - 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]
- Buccal swab test (genotyping for Gilbert's Syndrome)
- B-HCG pregnancy test
- Adverse Event Assessment

Baseline will be taken as measurements prior to the start of study treatment.

13.2 Run-in Period (Week -4 to Day -1)

The run-in period will begin once a subject has met the core eligibility criteria and will continue for 4 weeks. During this period, subjects will attend the site on Days -28, -21, and -14. Days -28, -21, and -14 will have a +/- 2 day window.

Research nurses or other appropriately qualified research personnel will assist with the administration of the SC APL-2 infusions at the Day -28 Visit (clinic visit) and will supervise the self-administration at a minimum on Day -25 (home or clinic visit), Day -21 (clinic visit) and Day -18 (home or clinic visit) or until the subject has been qualified to conduct self-administration. Following self-administration qualification, subjects may self-administer the SC infusions. The subject will continue to self-administer infusions at the clinic on those days when a clinic visit occurs and at an off-site location convenient to the subject on all other days.

The following assessments will be performed (*procedure not performed on Day -21):

- Eligibility confirmation
- Transfusion history
- Vaccinations
- Physical examination (Day -28 only)
- Triplicate 12-lead ECG
    - Day -28 only: Triplicate 12-lead ECG to be performed at -45, -30, and -15 minutes pre-dose (+/- 5 minutes for each measurement)

- APL-2 administration
- Eculizumab treatment
- Concomitant medications
- Vital sign measurements
- Urinalysis*
- Blood tests (see schedule of events for details)
- Hematology (Including reticulocytes), LDH
- Urine pregnancy test (Day -28 and Day -14 only)
- FACIT fatigue scale*
- Linear Analog Assessment Scale (LASA) for Quality of Life*
- EORTC QLQ-C30 Quality of Life questionnaire*
- Train subjects on APL-2 administration for self-administration qualification (Day -28 only)

After investigational product administration:

- Triplicate 12-lead ECG at 6 hours (+/- 30 minutes) post-dose (Day -28 only)
- Vital sign measurements at 30 minutes (+/- 5 minutes) post-dose
    - Day -28 (site visit) and Day -25 (home or clinic visit) only: vital sign measurements to also be measured at 2 (+/- 15 minutes), 4 (+/- 15 minutes), and 6 hours (+/- 30 minutes) post-dose
- PK sample at 6 hours (+/- 30 minutes) post-dose (Day -28 only)
- Adverse event assessment

13.2.1 Vaccinations

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 not previously documented, patients will also be vaccinated against *Haemophilus influenzae* Type B (Hib). Vaccination is mandatory unless documented evidence exists that subjects are non-responders to vaccination as evidenced by titers or display titer levels within acceptable local limits. The PI will discuss with the Sponsor in regard to individual patient circumstances.

Streptococcus pneumoniae vaccination requirement scenarios are as follows (unless documented evidence exists that subjects are non-responders to vaccination as evidenced by titers or display titer levels within acceptable local limits):

- If, within 2 years prior to initiating treatment with APL-2, the subject has documented *Streptococcus pneumoniae* vaccination with both the PCV13 vaccine and the PPSV23 vaccine, no additional *Streptococcus pneumoniae* vaccination is required for study entry.

- If, within 2 years prior to initiating treatment with APL-2, the subject has no documented *Streptococcus pneumoniae* vaccination with either the PCV13 vaccine or the PPSV23 vaccine, then the subject *must* receive the PCV13 vaccine within 2 weeks of Day 1, followed by the PPSV23 vaccine after at least 8 weeks, as indicated in the protocol.
- If, within 2 years prior to initiating treatment with APL-2, the subject has documented *Streptococcus pneumoniae* vaccination with the PCV13 vaccine *only*, then the subject *must* receive the PPSV23 vaccine within 2 weeks prior to Day 1, followed by a PPSV23 booster vaccine at least 8 weeks later.
- If, within 2 years prior to initiating treatment with APL-2, the subject has documented *Streptococcus pneumoniae* vaccination with the PPSV23 vaccine *only*, then the subject *must* receive the PPSV23 booster vaccine within 2 weeks prior to Day 1.

13.3 Randomized Controlled Period (Week 1 to Week 16)

13.3.1 Day 1

Following completion of the 4-week run-in period, subjects will enter the Randomized Controlled Period and will be randomized to either APL-2 or eculizumab. The following assessments outlined in the Schedule of Events (Section 4) will be performed:

Prior to randomization:

- Triplicate 12-lead ECG at -45, -30, and -15 minutes pre-dose (+/- 5 minutes for each measurement)
- Physical examination
- Concomitant medications
- Vital sign measurements
- Urinalysis
- Blood tests (see schedule of events for details)
- Urine pregnancy test
- FACIT fatigue scale
- LASA for Quality of Life
- EORTC QLQ-C30 Quality of Life questionnaire
- Dispense investigational product and infusion materials
- Train subject to perform home infusion
- Subjects will receive their last dose of APL-2 and may receive their last dose of eculizumab depending on their dosing schedule

Following investigational product administration:

- Triplicate 12-lead ECG at 6 hours (+/- 30 minutes) post-dose

- Vital sign measurements at 30 minutes (+/- 5 minutes), 2 (+/- 15 minutes), 4 (+/- 15 minutes), and 6 hours (+/- 30 minutes) post-dose
- PK sample at 6 hours (+/- 30 minutes) post-dose
- Collect Adverse Events

13.3.2 Week 1 to Week 16

Subjects will receive either eculizumab or self-administered twice-weekly SC doses 1,080 mg of APL-2 and will attend the investigator site at Weeks 1, 2, 4, 6, 8, 12, and 16 where the assessments outlined in the Schedule of Events (Section 4), will be performed.

Visit window: +/- 2 days, apart from Week 1 (no window).

The subject will continue to self-administer APL-2 infusions at the clinic on those days when a clinic visit occurs and at an off-site location convenient to the subject on all other days.

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

- Vital sign measurements (to be performed prior to ECG and venipuncture)
- Triplicate 12-lead ECG 15 minutes (+/- 5 minutes) pre-dose
    - Week 16 only: Triplicate 12-lead ECG at -45, -30, and -15 minutes pre-dose (+/- 5 minutes for each measurement)
- PK sample 15 minutes pre-dose to coincide with the pre-dose ECG
- Concomitant medications
- Adverse event review
- Urinalysis (not performed at Weeks 2 or 6)
- Blood tests (see schedule of events for details)
- Urine pregnancy test
- FACIT fatigue scale
- LASA for Quality of Life
- EORTC QLQ-C30 Quality of Life questionnaire
- Physical examination (Week 16 only)
- Vaccination (Week 2 only)
- Dispense investigational product and infusion materials
- Reconcile used investigation product returned by the patient
- Infuse investigational product or eculizumab

After investigational product administration:

- Triplicate 12-lead ECG at 6 hours (+/- 30 minutes) post-dose (Week 16 only)
- Vital sign measurements at 30 minutes (+/- 5 minutes) post-dose
    - Week 16 only: Vital sign measurements to be measured at 30 minutes (+/- 5 minutes), 2 (+/- 15 minutes), 4 (+/- 15 minutes), and 6 hours (+/- 30 minutes) post-dose
- PK sample at 6 hours (+/- 30 minutes) post-dose (Week 16 only)
- Collect adverse events

13.4 Open-Label Period (Week 17 to Week 48)

Subjects will receive self-administered twice-weekly SC doses of 1,080 mg of APL-2 and will attend the investigator site on Weeks 17, 18, 20, 22, 24 and every 4 weeks thereafter on Weeks 28, 32, 36, 40, 44, and 48 where the assessments outlined in the Schedule of Events (Section 4) will be performed.

Visit window: +/- 2 days, apart from Weeks 28 to 48 which have a +/- 7 day visit window

Subjects in Group 2 will receive APL-2 in addition to their eculizumab treatment from Weeks 17 to Week 20. At the end of Week 20 subjects will stop receiving eculizumab and continue receiving APL-2 through Week 48.

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

- Physical examination (Week 48 only)
- Vital sign measurements (to be performed prior to ECG and venipuncture)
- Triplicate 12-lead ECG 15 minutes (+/- 5 minutes) pre-dose
    - Week 48 only: Triplicate 12-lead ECG at -45, -30, and -15 minutes pre-dose (+/- 5 minutes for each measurement)
- PK sample 15 minutes pre-dose to coincide with the pre-dose ECG
- Concomitant medications
- Adverse event review
- Urinalysis (not performed at Week 17 or 22)
- Blood tests (see schedule of events for details)
- Urine pregnancy test
- FACIT fatigue scale
- LASA for Quality of Life
- EORTC QLQ-C30 Quality of Life questionnaire

- Dispense investigational product and infusion materials
- Reconcile used investigation product returned by the patient
- Infuse investigational product and/or eculizumab (until the end of Week 20, only)

After investigational product administration:

- Triplicate 12-lead ECG at 6 hours (+/- 30 minutes) post-dose (Week 48 only)
- Vital sign measurements at 30 (+/- 5 minutes) minutes post-dose
    - Week 48 only: Vital sign measurements to be measured at 30 minutes (+/- 5 minutes), 2 (+/- 15 minutes), 4 (+/- 15 minutes), and 6 hours (+/- 30 minutes) post-dose
- PK sample at 6 hours (+/- 30 minutes) post-dose (Week 48 only)
- Collect Adverse Events

At the completion of the Open-Label 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.

13.5 Follow-up (Week 54)

All subjects that complete study treatment and who do not participate in the open-label extension study will be asked to return to the investigator site for a follow-up visit 6 weeks after the Day 336 visit, on Day 378, where the assessments outlined in the Schedule of Events (Section 4) will be performed.

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

Visit window: +/- 7 days.

13.5.1 Exit Visit (Week 60)

All subjects who complete Follow-up (Week 54) will be asked to return to the clinical facility for the Exit Visit 12 weeks after the final dose of APL-2, on Day 420 (or sooner if the subject discontinues prior to the Week 48). 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, with the exception of investigational product administration.

Study participation for each subject will be concluded following completion of the Exit Visit. If a subject withdraws from the study prior to the scheduled Exit Visit, all Exit Visit evaluations should be performed at the subject's final visit to the clinic, including the collection of blood samples for PK and/or PD assessments, as well as a post-dose antigenicity sample if not yet collected.

Visit window: +/- 7 days.

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

13.5.2 Unscheduled Visits

Subjects may be asked to return to the clinical facility for additional visits if considered necessary by the PI or as relevant to subjects' dosing regimens.

Unscheduled visits may include (but are not limited to) any of the procedures listed in the Schedule of Events in Section 4. Examples of unscheduled visits include:

- Patient's return to the clinic to complete additional assessments and/or procedures at the discretion of the investigator
- Patient's return to the clinic for eculizumab dosing (based on patient's dose and dosing schedule)
- Patient's return to the clinic for APL-2 dosing (based on patient's dose, dosing schedule, and potential dose adjustments)

13.5.3 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will review cumulative safety/tolerability data (e.g., physical examinations, ECGs, vital signs, clinical laboratory tests, and adverse events), efficacy (Hb and LDH levels, haptoglobin level, reticulocytes counts, and RBC transfusions) and PK data. The DSMB will have the responsibility to conduct a thorough safety assessment at regular pre-defined intervals during the Randomized and Open-Label Treatment phases of the study.

The first DSMB meeting will be scheduled three months after the first subject is randomized, and at future intervals presented within the DSMB Charter. An *ad hoc* data review may be recommended by the DSMB or requested by the Sponsor at any time during the study.

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

13.6 Treatment Discontinuation and Study Withdrawal

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

1. Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, pregnancy, or other medical condition that indicates to the PI that continued participation is not in the best interest of the subject.
2. Subject's decision to withdraw.
3. Subject's failure to comply with protocol requirements or study-related procedures.
4. Termination of the study by the Sponsor, FDA, or other regulatory authorities.

The reason for treatment discontinuation and withdrawal from the study must be recorded in the subject's CRF.

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,

with the exception of investigational product 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.

If a subject is withdrawn from the study prior to study completion, the subject will undergo all procedures scheduled for study completion (Follow-up Visit and Exit Visit) as the situation allows. Any subject withdrawn due to an AE (whether serious or non-serious) or clinically significant abnormal laboratory test values will be evaluated by the investigator and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the PI.

14. ASSESSMENTS

14.1 Assessments

Assessments to be performed during the study are described below. Every effort should be made to ensure that the protocol-required assessments are completed as described.

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

14.1.1 Medical History

Medical history will be collected at the Screening Visit. Medical history relating to hemoglobin levels and pre-transfusion hemoglobin levels in the past year prior to study enrollment will be collected on Day -28.

14.1.2 Prior and Concomitant Medications

Treatment history of dose and duration of eculizumab will be collected in the past year prior to study enrollment. To be eligible for entry into the study, subjects will be receiving treatment with eculizumab, at a stable dose, for at least 3 months prior to screening. The dose of eculizumab will remain at this stable dose throughout the study except where eculizumab is discontinued during the Randomized Controlled Period for those randomized to APL-2 and at Week 20 for those randomized to eculizumab.

The number of PRBC transfusions within the 12 months prior to Day -28, including type and date of transfusion must be collected and documented in the CRF. Any transfusions received during the study will be clearly documented and will include type and date of transfusion.

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

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

14.1.3 Body Height and Weight

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

14.1.4 Physical Examination

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

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

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

14.1.5 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate will be measured prior to dosing as outlined in the Schedule of Events in Section 4. This will include an additional measurement to coincide with the second APL-2 administration during the Run-In Period (Day -25) by the health care professional conducting the self-administration qualification (see below for further clarification).

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

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

Additional monitoring of vital signs will occur as follows:

Day -28 (site visit), Day -25 (home or site visit), Day 1 (site visit), Week 16 (site visit), and Week 48 (site visit): pre-dose, 30 minutes (+/- 5 minutes), 2 (+/- 15 minutes), 4 (+/- 15 minutes) and 6 (+/- 30 minutes) hours post-dose.

At all other visits where APL--2 is administered at the study site, vital signs will be measured pre-dose and 30 minutes post-dose.

14.1.6 Electrocardiogram Monitoring

Triplicate 12-lead ECGs will be measured at the time points outlined in the Schedule of Events in Section 4 with three readings taken at least 1 minute and no more than 2 minutes apart. ECGs will be taken following resting in the supine position for 10 minutes in a quiet environment and prior to any blood sampling procedures.

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

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

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

The full set of ECGs should be sent as soon as possible to the ECG central laboratory for verification; if the QTcF (mean of QTcF replicate values) has declined to below 500 ms and is returning towards baseline, dosing may continue. If the mean QTcF remains ≥500 ms, the investigator, medical monitor, and cardiology consultant will assess the timing of additional ECGs and possible discontinuation of APL-2 dosing. Recommendation for discontinuation of APL-2 will be made on an individualized management plan based on the totality of the data. Since abrupt discontinuation of APL-2 could result in rebound hemolysis and an associated risk of thrombosis, attention will be directed towards avoiding unnecessary dosing interruptions and all decisions regarding dosing will be clearly documented.

ECGs will be sent to the central ECG laboratory for a treatment-blinded high-resolution measurement of the cardiac intervals and morphological assessment by a central cardiologist blinded to the study treatment. Please see the Study Operations Manual for further details on ECG collection, and reporting.

14.1.7 Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale

The FACIT Fatigue Scale is a 13 item Likert scaled instrument which is self-administered by the subjects during clinic visits as outlined in the Schedule of Events in Section 4. 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, some responses are reversed to ensure that the higher score corresponds to a higher quality of life. The FACIT Fatigue Scale and scoring guidelines are provided in Appendix 1 (Section 19.1).

14.1.8 Linear Analog Assessment Scale (LASA) for Quality of Life

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. A representation of the scale is presented in Appendix 2 in Section 19.2. Scores for the three individual components of the scale and the combined score will be included in the analysis and this will be described in the Statistical Analysis Plan.

14.1.9 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 patient QOL/overall perceived health status. Scoring guidelines from EORTC will be used to calculate patients' scores. The QLQ-C30 and scoring guidelines are provided in Appendix 3 in Section 19.3.

14.1.10 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Schedule of Events in Section 4. In addition, laboratory safety tests may be performed at various unscheduled time points, if

deemed necessary by the PI or recommended by the DSMB. The clinical laboratory tests include (but are not limited to) the following:

14.1.10.1 Hematology

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

14.1.10.2 Coagulation

- Prothrombin time (PT)
- Fibrinogen
- Activated partial thromboplastin time (aPTT)
- D-Dimer

NOTE: The use of silica reagents in coagulation panels should be avoided in subjects treated with APL-2.

14.1.10.3 Serum Chemistry

- Blood urea nitrogen (BUN)
- Creatinine
- Estimated creatinine clearance (using Cockcroft-Gault formula) –screening only
- Bilirubin (total and direct)
- Albumin
- Alkaline phosphatase (ALP)
- Lactate dehydrogenase (LDH)
- Haptoglobin
- Gamma-glutamyl transpeptidase (GGT)
- Lactate Dehydrogenase Isoenzymes
- Vitamin B12
- Creatine kinase (CK)
- Aspartate aminotransferase (AST)
- Alanine Aminotransferase (ALT)
- Uric acid
- Glucose
- Sodium
- Potassium
- Chloride
- Ferritin
- Erythropoietin
- Folate
- Calcium
- Phosphate

14.1.10.4 Urinalysis

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

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

Samples for genotyping (for Gilbert's Syndrome) will be obtained via buccal swab tests done at the Screening Visit.

14.1.10.5 Human Chorionic Gonadotropin (Serum Pregnancy Test) and Follicle-Stimulating Hormone

Serum Pregnancy Test will be performed for females only. Follicle-Stimulating Hormone (FSH) will be performed for postmenopausal females at screening only.

14.1.11 Injection/Infusion Site and Pump Safety Assessment

On the days of clinical visits, an assessment of the APL-2 injection site and pump use safety will be performed within 30 minutes after study drug administration. The assessment will be performed by a physician or other licensed health care provider (e.g., study nurse) as delegated by the investigator. The injection site and surrounding area will be inspected for redness, swelling, induration, and bruising. The subject will be asked about the presence of pain and/or tenderness, and any issue related to pump use. The date, time, and outcome of the injection site assessment will be recorded on the source documents and CRFs.

Subjects will be instructed to notify the PI or other study personnel in the event that an injection site reaction occurs after self-administration of APL-2. All clinically relevant adverse events, as determined by the investigator, from injection site or related to pump use will be recorded as AEs.

14.2 Pharmacokinetic Assessments

14.2.1 Blood Sampling and Processing

Blood samples for PK assessment of APL-2 will be collected via direct venipuncture at the time points delineated in the Schedule of Events in Section 4.

On Day -28, Day 1, Week 16, and Week 48 only, PK samples will be taken pre-dose and at 6 hours post-dose (+/- 30 minutes). PK samples will be taken 15 minutes pre-dose at all other visits, to coincide with the pre-dose ECG monitoring.

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

14.2.2 Analytical Method

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

14.3 Flow Cytometry Assessments

Blood samples for flow cytometry assessment will be collected via direct venipuncture at the time points delineated in the Schedule of Events in Section 4. Flow cytometry assessment will include, but not be limited to: PNH clonal distribution of RBCs, PNH clonal distribution of immature reticulocytes (CD71+), monocytes and granulocytes and C3 deposition on RBCs.

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

14.4 Pharmacodynamic Assessments

Blood samples will be collected via direct venipuncture at the time points delineated in the Schedule of Events in Section 4 for PD assessment of complement activation through the classical (i.e., CH50) and alternative (i.e., AP50) pathways. Blood samples will also be collected to measure C3 levels. Other relevant PD markers may also be assessed.

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

The PD sample analysis plan will be provided as a separate document.

14.5 Anti-APL-2 Antibody Assessment

Follow patients who test positive for anti-APL-2 antibodies until the antibody levels revert to baseline and characterize their antibodies for titer, binding to the cyclic pentadecapeptide and PEG domains, and the neutralizing capacity.

Patients who discontinue dosing will need to have anti-drug antibody (ADA) samples collected at their Follow-up visits (Week 54 and Week 60).

Patients who test positive for anti-APL-2 antibodies at any time will be followed with ADA samples being collected every 6 months until the antibody levels revert to baseline. Samples that test positive will be characterized by an assay that will determine antibody titer, binding to the cyclic peptide or PEG domains, and measure neutralizing capacity.

The proposed ADA sampling schedule was established to capture the ADA signal at baseline, along with any potential early onset and the dynamic profile (transient or persistent) of antibody formation while minimizing APL-2 level in the sample.

14.6 Blood Volume for Study Assessments

Table 1: Blood Volume During Study

Assay	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Pharmacokinetics	27	5	135
Anti-APL-2 Ab assay	8	5	40
Hematology	24	4	96
Chemistry (Incl. screen pregnancy)	24	12	288
Coagulation profile	8	6	48
Complement profile (C3, CH50, and AP50)	22	8	176
Flow cytometry, PNH clones and C3 deposition	15	2	30
Plasma (free) Hb	17	6	102
Direct Coombs	17	3	51
Total Approximate Blood Volume For Study:			**966***

*Represents the standard collection volume planned over the duration of the study, actual volume may vary.

NOTE: The use of silica reagents in coagulation panels should be avoided in subjects treated with APL-2.

14.7 Pregnancy Tests

For WOCBP, a serum pregnancy test will be performed at screening, and subjects with a positive test will be excluded from the study. A follow up urine pregnancy test will be performed on Day -28 pre-dose (a negative urine pregnancy test must be received before dosing with study drug). A urine pregnancy test will also be performed at each site visit (pre-dose) if applicable. A final urine pregnancy test will be performed at the final Exit Visit. Male subjects will be counseled to avoid donating sperm during the time between the first dose on Day -28 and the final Exit Visit and 90 days after their last dose of study drug.

15. ADVERSE EVENTS

15.1 Definition

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign, including a clinically significant abnormal laboratory finding, symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug (United States Food and Drug Administration [FDA] guidance, December 2012). Any abnormal laboratory finding that is deemed not clinically significant is not an AE.

Adverse events include the onset of new illness and the exacerbation of pre-existing conditions. Any medical condition that is present at the time that the subject is screened should be recorded on the medical history eCRF and not reported as an AE. However, if that condition deteriorates or severity changes at any time during the study, it should be recorded as an AE.

Any AEs that occur prior to dosing on Day -28 will be categorized as pre-treatment events. TEAEs will be defined as those AEs that occur after dosing on Day -28 or worsen in severity.

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

15.2 Recording Adverse Events

All AEs encountered during the study will be monitored and reported in detail in the source documents and documented on the eCRF, from signing of the ICF until the Exit Visit. AEs, especially those for which the relationship to test drug is considered by the PI to be possibly or probably related, should be followed up until they have returned to the baseline status or stabilized. If a clear explanation is established, it should be recorded on the eCRF.

Subjects will be monitored throughout the study for adverse reactions to the study formulations and/or procedures. Subjects will be asked how they are feeling at each Study Visit.

AEs (whether serious or non-serious) including clinically significant abnormal laboratory test value(s) will be evaluated by the PI and treated and/or followed up until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI.

When appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as recovered/resolved, recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved, fatal or unknown (lost to follow-up).

15.3 Treatment and Follow-up of Adverse Events

AEs (whether serious or non-serious), including clinically significant abnormal laboratory test values, will be evaluated by the Investigator and treated and/or followed up until the symptoms or value(s) return to baseline or are clinically stable. Treatment of AEs will be performed by appropriately trained medical personnel, either at the clinical site or at a nearby hospital

emergency room. When appropriate, medical tests and/or examinations will be performed to document resolution of the event(s).

AEs continuing after completion of the study will be followed up by telephone or with visits per the discretion of the Investigator. If possible, the outcome of any AE that caused discontinuation from the study or was present at the end of the study should be reported, particularly if the AE was considered by the PI to be related to the study drug.

15.4 Reporting

The collection of clinical information will begin after the subject's written consent to participate in the study has been obtained. AEs will be collected after signing the ICF through to completion of the Exit Visit. Any events that occur prior to dosing on Day -28 will be categorized as pre-treatment events. Events occurring after dosing on Day -28 will be recorded as TEAEs. AEs may be either spontaneously reported or elicited during questioning and examination of a subject.

All identified AEs, including clinically significant laboratory findings, must be recorded and described on the appropriate AE page of the eCRF, or (if applicable) the SAE form. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. AEs will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA®) coding dictionary.

Subjects experiencing AEs that cause interruption or discontinuation of study drug, or those experiencing AEs that are present at the Exit Visit should receive follow-up as appropriate. If possible, the outcome of any AE that caused permanent discontinuation or was present at the end of the study should be reported, particularly if the AE was considered by the PI to be related to the study drug.

15.4.1 Relationship of Events to Study Treatment

All AEs that occur during this study will be recorded. The PI will review each event and assess its relationship to study drug treatment (definitely related, possibly related, unlikely related, not related, unknown). The date and time of onset, time relationship to drug dosing, duration, and outcome (recovered/resolved, recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved, fatal or unknown [lost to follow-up]) of each event will be noted.

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

Definitely Related	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary

Possibly Related	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely Related	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Not Related	• Event or laboratory test abnormality, is plausibly related to the participant's clinical state, underlying disease, or the study procedure/conditions • Time relationship to drug intake makes a relationship unreasonable • Other obvious causes for event or laboratory test abnormality exist
Unknown	• Report suggests an adverse event, however, cannot be judged at this time because information is insufficient or contradictory • More data for proper assessment is needed, or additional data is under examination

15.4.2 Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate	Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*.
Severe	Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**. Note: An experience may be severe but may not be serious, e.g., severe headache).

A semi-colon indicates 'or' within the description of the grade.

Note: Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

15.5 Serious Adverse Events

If any AEs are serious, special procedures will be followed. All SAEs will be reported to the Safety Monitor (Synergy) by the PI via fax or email within one calendar day of becoming aware of the event, whether or not the serious events are deemed drug-related. SAE reporting contact information will be provided separately and as included in the Safety Monitoring Plan. All SAEs must be reported to the applicable ethics committee by the PI in accordance with their regulations.

An SAE is any adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, results in any of the following outcomes: death, a life-threatening

adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

Unexpected is defined as an AE or suspected adverse reaction that is not listed in the IB or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

15.6 Unexpected Adverse Events or Unexpected Suspected Adverse Reactions

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of increased severity) if the IB referred only to elevated hepatic enzymes or hepatitis.

The Sponsor will be responsible for reporting any serious and unexpected adverse events to the applicable regulatory agencies as required.

15.7 Pregnancy

Although pregnancy is not considered an AE, the outcome of a pregnancy, if there is a spontaneous abortion, congenital anomaly or other adverse fetal outcome, may be an SAE. All SAEs are to be reported to the study Sponsor on the SAE Reporting Form.

WOCBP and males with female partners of child-bearing potential will be instructed to practice an acceptable method of birth control (as defined in Section 11.1.1) for the duration of the study.

If a female subject or partner of a male subject becomes pregnant during the study or during the 90 days following last dose of APL-2, the PI should report the pregnancy to the Safety Monitor (Synergy) using the Pregnancy Report Form within one calendar day of being notified. The subject or partner of a male subject should be followed by the PI until completion of the pregnancy. At the completion of the pregnancy, the PI will document and report the outcome. If the outcome of the pregnancy meets the criteria for classification as an SAE (i.e. postpartum complication, stillbirth, neonatal death, or congenital anomaly) the PI should follow the procedures for reporting an SAE (Section 15.4).

16. STATISTICS METHODS

16.1 Sample Size Justification

A sample size of 64 randomized subjects (32 in each group) provides 90% power (using a 2-sided 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 of 1 g/dL and a standard deviation for the change from baseline of 1.2 g/dL. 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 1.4 g/dL, the power is reduced to 80%. Consequently, a blinded sample size re-assessment may be performed prior to the completion of study enrollment. 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.

16.2 Preservation of Type 1 Error

To preserve the Type 1 error a fixed sequence testing strategy will be used. All tests will be performed at the 0.05 level following the pre-specified order. The key secondary and secondary endpoints will be tested in a hierarchical manner after statistical significance is reached for the primary endpoint. Once one hypothesis is tested and found not to be statistically 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.

16.3 Statistical Analysis Methodology

A formal Statistical Analysis Plan (SAP) will be developed and finalized prior to locking the database. The full details of data presentations and analyses will be provided in the SAP. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and included in the SAP. Any deviations from the final SAP or from what is outlined in the protocol will be discussed in the final study report.

All endpoints will be summarized by treatment group and visit. Continuous data will be summarized using descriptive statistics (e.g., mean and standard deviation) and categorical data will be summarized using frequency tables (counts and percentages).

16.3.1 Analysis Sets

16.3.1.1 Screened Set

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

16.3.1.2 Run-in Set

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

16.3.1.3 Safety Set

The safety set will include all randomized subjects and received at least 1 dose of study drug.

16.3.1.4 Intent-to-Treat (ITT) Set

The ITT set will include all randomized subjects.

16.3.1.5 Modified Intent-To-Treat (mITT) Set

The mITT will include all subjects in the ITT set who continue study treatment into the Randomized Controlled Period (i.e., beyond their Week 4 visit).

16.3.1.6 Per Protocol (PP) Set

The PP set will include all subjects in the ITT set who have not violated any inclusion or exclusion criteria and/or deviated from the protocol, in a way that could influence their efficacy assessment. Decisions concerning the exclusion of subjects from the per protocol analysis set will be made and documented prior to database lock.

16.3.1.7 Pharmacokinetic (PK) Set

The PK set will include all subjects in the ITT set who receive APL-2 and have at least 1 evaluable post-dose PK measurement.

16.3.1.8 Pharmacodynamic (PD) Set

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

16.3.1.9 Data Review for Analysis Sets

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

16.3.2 Efficacy Analyses

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

All possible efforts will be made to ensure that subjects complete all the required assessments. As missing data may potentially bias the outcome of the statistical analyses and the subsequent

estimation of the magnitude of the treatment effect, different strategies will be applied to provide a balanced assessment of treatment efficacy.

Endpoints will be summarized and, where appropriate, plotted over time for each treatment group.

Baseline will be taken as the average of measurements prior to the start of study treatment.

16.3.2.1 Primary Endpoint

For the primary analysis, missing Hb levels will be imputed using the technique of multiple imputations, under the assumption that Hb levels are missing at random (MAR). If a subject receives a transfusion during their treatment period the pre-transfusion Hb value (central or local laboratory reading) will be used in the calculation of the primary endpoint as their Week 16 value.

For each imputed dataset, the Week 16 change from baseline will be calculated and then analyzed using analysis of covariance (ANCOVA). Stratification variables will be included as covariates. Baseline Hb will be included as a continuous covariate. Combining the results from these individual analyses the difference between treatment groups will be estimated, along with its 95% confidence interval and p-value.

The following will be included as sensitivity analyses:

- The primary efficacy endpoint, change from Baseline to Week 16 in Hb level, will be analyzed using mixed model for repeated measures (MMRM) with the effects of treatment; stratification randomization; study visit, study visit-by-treatment interaction; baseline Hb level and baseline Hb level-by-visit interaction using an unstructured covariance matrix. The difference between treatment groups will be estimated, along with its 95% CI and p-value.

  If a subject receives a transfusion during their treatment period, the Hb levels up to the pre-transfusion will be included in the model.

- an analysis using the PP set
- an analysis using the mITT set, i.e., excluding those subjects who withdraw prior to Week 4
- an analysis using all available data, regardless of whether the Hb measurement was following a transfusion
- an analysis imputing the subject's lowest recorded Hb level for missing values, where the missingness of the data is considered as informative. Multiple imputation will be used for cases where it is not considered informative.
- an analysis including only those subjects who complete the 16 weeks of randomized treatment
- tipping point analyses where alternative Week 16 levels of hemoglobin are imputed following a transfusion

16.3.2.2 Key Secondary Endpoints

The key secondary endpoints analyses will be performed on the ITT set and will be repeated on the PP set.

The key secondary and secondary endpoints will be tested in a hierarchical manner after statistical significance is reached for the primary endpoint.

1) The proportion of patients with transfusion avoidance will be provided for both treatment groups. Also, the difference in the proportion of patients with TA between APL-2 and eculizumab and its 95% CI will be calculated. If the lower bound of the 95% CI for the difference in the proportion of patients with TA between APL-2 and eculizumab is greater than the non-inferiority margin of -20%, then APL-2 will be considered to be non-inferior to eculizumab and the next endpoint will be tested.

2) The change from Baseline to Week 16 in reticulocyte count will be analyzed using the same method as the primary efficacy endpoint. If the upper bound of the 95% CI for the difference between APL-2 and eculizumab treatment groups in the change from baseline in reticulocyte count is less than the non-inferiority margin of 10, then APL-2 will be considered to be non-inferior to eculizumab and the next endpoint will be tested.

3) The change from Baseline to Week 16 in LDH will be analyzed using the same method as the primary efficacy endpoint. If the upper bound of the 95% CI for the difference between APL-2 and eculizumab treatment groups in the change from baseline in LDH is less than the non-inferiority margin of 20, then APL-2 will be considered to be non-inferior to eculizumab and the next endpoint will be tested.

4) The change from Baseline to Week 16 in FACIT-fatigue score will be analyzed using the same method as the primary efficacy endpoint. If the lower bound of the 95% CI for the difference between APL-2 and eculizumab treatment groups in the change from baseline in FACIT-fatigue score is greater than the non-inferiority margin of -3, then APL-2 will be considered to be non-inferior to eculizumab and the next endpoint will be tested.

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.

16.3.2.3 Secondary Endpoints

For the responder (Yes/No) endpoints of reticulocyte normalization and hemoglobin response, in the absence of transfusions, the number and percentage of subjects who respond 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 & Nurminen method.

The number and percentage of subjects achieving hemoglobin normalization 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 & Nurminen method. Subjects who receive a transfusion prior to Week 16 will be analyzed as non-responders.

Analyses for Week 16 change from baseline endpoints will use the same methods described for the primary analysis of the primary endpoint, except also using their own baseline as a covariate.

Endpoints during the open-label APL-2 period will be analyzed using similar methods described for endpoints during the randomized treatment period.

16.3.3 Safety Analyses

All safety endpoints will be evaluated using the Run-In and Safety Sets.

Safety summaries will be presented over the run-in period, 16 weeks of randomized treatment and 32 weeks of open-label treatment, as well as the overall duration of the study.

16.3.3.1 Adverse Events

Treatment emergent adverse events are defined as those AEs that develop or worsen after the first dose of study medication and up to 30 days beyond the last dose of study medication. The current version of MedDRA will be used to classify all AEs.

Treatment-emergent adverse events will be summarized by System Organ Class and Preferred Term, in accordance with the MedDRA coding dictionary. The number of subjects reporting each AE preferred term will be tabulated for all TEAEs and separately for those considered as possibly related to study treatment by the Investigator. Number of subjects reporting SAEs will also be tabulated. Adverse event summaries will be presented for each period of the study (run-in, randomized treatment and open-label APL-2) separately within each treatment group.

The number of subjects reporting thromboembolic events will be tabulated for each period of the study separately within each treatment group.

16.3.3.2 Clinical Laboratory Tests

Changes from baseline in laboratory will be summarized using descriptive statistics by treatment, visit and nominal time post dose. Baseline will be taken as the last measurement prior to the first dose of APL-2.

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

16.3.3.3 Vital Signs and ECGs

Changes from baseline in vital signs and ECG parameters will be summarized using descriptive statistics by treatment, visit and nominal time post dose. Baseline will be taken as the last measurement prior to the first dose of APL-2.

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

ECG parameters will be analyzed using concentration effect models.

16.3.4 Pharmacokinetic Analyses

The PK concentrations will be evaluated using the PK Set.

Concentrations will be summarized using descriptive statistics over time for the run-in period (all subjects) and the randomized treatment period (APL-2 group).

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

Population pharmacokinetic and exposure-response modelling of the safety and efficacy data will be described in an APL-2 Population Pharmacokinetic/Pharmacodynamic Analysis Plan. The methods will be based on the FDA Guidances for both Exposure-Response and Population Pharmacokinetics (FDA Guidance for Industry Population Pharmacokinetics; FDA Guidance for Exposure-Response Relationships).

16.3.5 Pharmacodynamic Analyses

The PD endpoints will be evaluated using the PD Population.

Absolute values, changes from baseline and % changes from baseline will be summarized using descriptive statistics over time for the run-in period (all subjects) and the randomized treatment period by treatment group.

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

The PD endpoints will be compared between treatment groups using mixed effect repeated measures analyses.

16.3.6 Other Data Analyses

Demographic data, baseline characteristics, physical examination, concomitant medication, medical history data and study medication exposure will be summarized by treatment group.

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

16.4 Interim Analyses

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 and the database has been cleaned for all visits up to and including Week 16.

A blinded sample size re-assessment may be performed prior to the completion of study enrollment.

16.5 Direct Access to Source Data/Documents

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

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

16.6 Quality Control and Quality Assurance

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

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

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

16.6.1 Monitoring

On-site monitoring will be performed by the Sponsor's designee for the duration of the study. The monitor will ensure that the study is conducted, recorded and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirements. The monitor will verify the accuracy and completeness of the eCRF entries, source documents, and other study-related records against each other. The PI will provide direct access to source data/documents for study-related monitoring. It is important that the PI and the staff are available at these visits. The monitor will record the date of each visit together with a summary of the status and progress of the study. Proposed actions will be documented in writing to the PI.

17. ETHICS

17.1.1 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, applicable regulations, the ethical principles set forth in the Declaration of Helsinki, and the ICH Harmonized Tripartite Guidance for Good Clinical Practice, E6, R1 (ICH GCP).

17.1.2 Institutional Review Board/Ethic Committee

The study protocol, any amendments to the protocol, informed consent form, the Investigator's Brochure, and other study specific information will be reviewed and approved by the IRB/IEC. The study will not be initiated until the IRB/IEC has approved the protocol or a modification thereof. All records pertaining to IRB/IEC submission and approval should be kept in the site's regulatory files and Sponsor's Trial Master File (TMF).

The IRB/IEC must be constituted and operate in accordance with the all applicable regulatory requirements.

17.1.3 Subject Information and Consent

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

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

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

17.1.4 Confidentiality

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

17.1.5 ClinicalTrials.gov

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

17.1.6 Termination of Study

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

17.2 Data Handling and Record Keeping

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

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

17.3 Protocol Amendments

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

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

17.4 Report Format

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

17.5 Finance and Insurance

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

17.6 Publication Policy

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

Apellis will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Apellis adheres to external guidelines (e.g., Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Apellis. The

purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

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

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

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

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

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

18. REFERENCES

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