Protocol No.: APL-CP0514

An Open Label, Single and Multiple Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of APL-2 as an Add-On to Standard of Care in Subjects with Paroxysmal Nocturnal Hemoglobinuria (PNH).

Phase: 1

Version: Version 4.0, Amendment 7

Date: June 15, 2017

1. SYNOPSIS

Protocol Number	APL-CP0514
Protocol Version and Date	Version 4.0 Amendment 7 June 15, 2017
Compound	APL-2
Study Phase and Type	Phase 1, open-label, prospective, non-randomized, single and multiple ascending dose, first-in-human study in patients with PNH
Study Objectives	The primary objectives of the study are to assess the safety, tolerability and pharmacokinetics of single and multiple subcutaneous (SC) doses of APL-2 in subjects with paroxysmal nocturnal hemoglobinuria (PNH) who are still anemic after treatment with eculizumab (Soliris®). An exploratory objective of the study is to assess the pharmacodynamics (PD) of single and multiple SC doses of APL-2 when administered to PNH patients. See "Pharmacodynamic Assessment" below.
Study Population	Subjects will: • be male and female (using contraception as specified in the protocol) at least 18 years of age • have a diagnosis of PNH and still be anemic (after being treated with eculizumab (Soliris®) for at least 3 months prior to screening.
Number of Subjects	The study is planned to enroll approximately 15 subjects across 4 Cohorts. Cohorts 1-3 will comprise 2 subjects in each cohort. Cohort 4 will enroll sufficient subjects to ensure at least 6 subjects complete 28 days dosing with APL-2. Subjects may participate in more than one cohort. Additional cohorts may be enrolled if it is deemed appropriate by the Sponsor in consultation with the Safety Monitoring Committee (SMC) to repeat a dose level or to study an interim dose level.

Inclusion Criteria

- Male or Female
- At least 18 years of age
- Weigh >55 kg
- Diagnosed with PNH
- On treatment with eculizumab (Soliris®) for at least 3 months
- Hb <10 g/dL at screening OR have received at least one transfusion within 12 months prior to screening
- Platelet count of >30,000/mm^3
- Absolute neutrophil count >500/mm^3
- Women of child-bearing potential (WOCBP) must have a negative pregnancy test at screening and must agree to use protocol defined methods of contraception for the duration of the study
- Males must agree to use protocol defined methods of contraception and agree to refrain from donating sperm for the duration of the study
- Willing and able to give informed consent

Exclusion Criteria

- Active bacterial infection
- Known infection with hepatitis B, C or HIV
- Hereditary complement deficiency
- History of bone marrow transplantation
- Participation in any other investigational drug trial or exposure to other investigational agent, device or procedure within 30 days
- Evidence of QTcF prolongation defined as >450 ms for males and >470 ms for females at screening
- Creatinine clearance (CrCl) <50 mL/min (Cockcroft-Gault formula) at screening
- Breast-feeding women
- History of meningococcal disease
- No vaccination against *N. meningitides* types A, C, W, Y and B (administered as two separate vaccinations), Pneumococcal conjugate vaccine or Pneumococcal polysaccharide vaccine 23 (PCV13 or PPSV23, respectively) and *Haemophilus influenzae* Type B (Hib) vaccination within 2 years prior to Day 1 dosing.

Endpoints

The primary endpoints of the study are the number and severity of TEAEs and pharmacokinetics parameters of APL-2 following administration of

single and multiple SC doses.

Exploratory pharmacodynamics markers include:

- Complement (e.g., CH50, AH50, and C3) levels
- C3 deposition on RBC cells
- Hemoglobin
- Reticulocytes
- Lactate dehydrogenase (LDH)
- Bilirubin
- Clonal distribution of PNH vs normal bone marrow derived cells

Planned Dose Levels

Planned doses will be as follows:

Cohort	Planned dosing schedule (Amendment 5)
1	25 mg on Day 1 then 5 mg/day from Day 29 to Day 56
2	50 mg on Day 1 then 30 mg/day from Day 29 to Day 56
3	180 mg/day from Day 1 to Day 28
4	270 mg/day from Day 1 to Day 729* with optional intrasubject escalation up to 360 mg/day after Day 28**

*Subjects may initially receive APL-2 for 28 days (Part 1) and if there is evidence of clinical benefit they may continue to receive APL-2 until Day 84 (Part 2A) and if there is ongoing evidence of clinical benefit they may continue to receive APL-2 until Day 364 (Part 2B). If subjects continue to have clinical benefit they may receive APL-2 until Day 729 (Part 2C).

** Individual patient dose escalation up to a dose of 360 mg/day may occur in subjects who have a sub-optimal hematological response but acceptable tolerability.

Repeat of any cohort or the addition of interim dose level may be added, as determined by the Sponsor in consultation with the Safety Monitoring Committee (SMC), depending on the safety results from the prior cohort(s).

Study Design

This is a prospective, non-randomized, single and multiple ascending dose study. Four Cohorts are planned for evaluation. Subjects in Cohorts 1 and 2 will receive a single dose of APL-2 followed by a 28-day waiting period before receiving daily doses for 28 days. Subjects in Cohort 3 will receive multiple doses (daily dosing) for 28 days. Subjects in Cohort 4 will receive multiple doses (daily dosing) for 28 days and if, following review of available safety and PD data available

within the first 28 days, subjects have shown evidence of clinical benefits, as assessed by the Investigator and Sponsor, they may progress to Part 2A of the study and continue to receive daily doses of APL 2 until Day 84 and to Part 2B of the study and continue to receive daily doses of APL-2 until Day 364. If subjects continue to have clinical benefit they may receive APL-2 until Day 729 (Part 2C). Subjects may participate in more than one cohort.

Safety will be assessed throughout the study; serial blood samples and urine samples will be collected for these assessments. Blood samples will also be collected for the PK assessment of APL-2. Additional samples for assessment of PD will also be collected. Interim PK analyses may be performed to reconsider the sampling time points and dose escalations as the study progresses.

For prior study design including the dosing schedule for Cohorts 1 to 3, refer to prior versions of the protocol.

Subjects in Cohort 4 will initially receive 270 mg SC APL-2 daily for 28 days. Subjects will be entered into the study at Visit 2 (Day 1) at a time designated by the PI and will receive daily SC doses of APL-2 at Visits 2 to 29 (Days 1 to 28). The first 4 daily SC doses of APL-2 (Visits 2 to 5) as well as doses at Visits 9, 16 and 23 will be administered at the clinical site. Subjects will remain in the clinic for at least 4 hours after the first dosing at Visit 2.

Following ongoing review of available safety, PK and PD data by the Investigator and Sponsor, subjects showing evidence of clinical benefit may progress to Part 2A, then to Part 2B and then to Part 2C of the study and may continue to receive daily doses of APL-2 until Day 84, then until Day 364, and then until Day 729. Doses will be administered off-site at the subject's home, workplace, or other location convenient to the subject, with the exception of Visits 30, 44, 58, 72, 86, 114, 142, 170, 198, 226, 254, 282, 310, 338, 366, 367, 368, 369, 370, and 371 (Days 29, 43, 57, 71, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 420, 476, 532, 616, and 729 respectively) and with the exception of up to 3 additional site Visits, if individual dose escalation occurs for subjects administered >270 mg/day SC APL-2, where dosing will occur at the clinical site. After conclusion of the Part 2C treatment period on Visit 371 (Day 729), subjects will return to the clinical site for final study procedures at an Exit Visit on Day 785 See Study Flow Chart.

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AMENDMENT 1

Revision 1: Inclusion Criteria #1: The upper age limit of 65 years for inclusion will be removed.

Rationale: Although the median age of the 1610 patients enrolled in the international PNH registry (as of June 30, 2012) was 42 years old; the range is 3 to 99 years old (Schrezenmeier, 2014). This update to the inclusion criteria will allow collection of data on APL-2 across a wider range of the adult PNH population and better support subsequent clinical studies.

Section updated: Section 7.1

Revision 2: Inclusion Criteria #6 and #7: Hemoglobin (Hb) level and transfusion inclusion criteria were combined into a single criterion to allow patients with Hb <10 g/dL at screening OR at least one transfusion within the last 12 months.

Rationale: The previous inclusion criteria requiring pre-transfusion Hb<10 g/dL at the last transfusion AND last transfusion within 12 months prior to screening is causing confusion. The pre-transfusion Hb value is not always available to the investigator and a value of <10 g/dL is implicit as the criteria for transfusion in PNH subjects is generally Hb<10 g/dL. The addition of Hb <10 g/dL at screening ensures that subjects are still anemic despite treatment with Soliris® even if they have not received a transfusion in the past year.

Section updated: Section 7.1

Revision 3: Exclusion Criteria #7: Creatinine clearance (CrCl) (Cockcroft-Gault formula) will be amended from <60 mL/min to <50 mL/min.

Rationale: Mild to moderate reduction in glomerular filtration rate (GFR) is commonly seen in the PNH patient population. Report from Phase III studies with Soliris® indicate that 65% of patients presented renal dysfunction (GFR <60 mL/min/1.73m^2) at baseline with 21 % of patients being at the later stage of Chronic Kidney Disease (CKD) or kidney failure. Whereas approximately 30% of patients improve after treatment with Soliris® (mostly those with Stage 1 or 2 CKD), close to 70% of patients do not improve and can even worsen (Hillmen, 2010). This is of relevance as the target population for this current trial is patients who are not fully responding to Soliris®. A reduction in the minimum CrCl required for inclusion will allow patients with moderate reduction in GFR (CKD Stage 3A) to participate in the study while more severe GFR reductions (CKD Stages 3B to 5) will continue to be excluded.

Section updated: Section 7.2

Revision 4: Multiple doses for cohort 2, 3 and 4 will be updated as follows:

	Single SC dose (day 1) Unchanged	Multiple SC dose (days 29 to 56) Original Protocol	Multiple SC dose (days 29 to 56) Amendment 1
Cohort 1	25 mg APL-2	5 mg APL-2 / day	5 mg APL-2 / day
Cohort 2	50 mg APL-2	10 mg APL-2 / day	**30 mg APL-2 / day**
Cohort 3	100 mg APL-2	20 mg APL-2 / day	**90 mg APL-2 / day**
Cohort 4	200 mg APL-2	40 mg APL-2 / day	**180 mg APL-2 / day**

Rationale: The doses were updated based on emerging safety, pharmacokinetic and pharmacodynamics data from ongoing studies in healthy subjects currently conducted in Australia summarized in section 4.1.2.2.2. Rationale for this change is described in the updated Section 4.2.2 of this document.

Sections Updated: Sections 4.1.2.2.2, 4.2.2 and 8.3.2

Revision 5: Description of the investigational product has been updated to include a lyophilized product formulation to be used for the higher doses.

Rationale: For reasons of stability and flexibility, the drug product is now being produced as lyophilized vials that are reconstituted just prior to administration. This new presentation will be used for the repeated dose portion of the trial at the higher doses.

Section updated: Section 8.3.1

Revision 6: Removal of pre-defined stopping rules and creation of an independent Safety Monitoring Committee (SMC).

Rationale: Previously, the transition to multiple dosing and escalation to the next cohort would occur only after review of safety data for **both** subjects in the preceding cohort. This is problematic as both patients in a cohort would need to be scheduled to commence dosing in parallel on the same day, which is unfeasible given the low numbers of patients with PNH. Otherwise, it would result in every patient having a different window between single and multiple dosing and consequently being enrolled into study for different lengths of time. This creates a logistical challenge for the sites and makes comparison of data across patients very difficult.

The new dose escalation scheme will follow the same schedule as previously stipulated (i.e. 28 days between single and multiple dosing). However:

The transition to multiple dosing within a subject will occur automatically once the subject has completed the 28-day waiting period.

Dose escalation and initiation of a subsequent cohort will only occur once both subjects in the preceding cohort have completed the single-dose 28-day waiting period.

The above transitions would not occur if modification, or stopping of the study, is proposed by the SMC following their regular review.

An independent SMC will be convened to include at minimum a hematologist with PHN experience and an infectious disease specialist. The SMC decisions will not be guided by pre-defined stopping rules as they will have total authority to stop any dose escalation (or the study) at any time because of any safety concern beyond the pre-defined incidence of SAEs or Grade 3 toxicities. The SMC will meet every 4 weeks and review all available cumulative safety, PK and PD data. The SMC meeting will not always coincide with the dose escalations but this high frequency review of cumulative data will provide assurance of ongoing patient safety.

Section Updated: Section 9.3

Revision 7: Addition of an Adverse Events of special interest section.

Rationale: This section includes AE of scientific and medical concern specific to the product or program where ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. In addition, occurrence of these AEs will be presented separately to the SMC.

Section Updated: Section 11.5

Additional Revisions: Editorial changes have been made throughout the protocol for clarity or corrections.

Amendment 2

Revision 1: Inclusion Criteria #3: The weight and BMI criteria have been revised.

Rationale: The weight and BMI restriction has significantly limited the number of patients eligible to participate in this clinical study. Preliminary pharmacokinetic (PK) data from ongoing studies suggests that the impact of this update will be negligible with respect to exposure. This update to the inclusion criteria will allow collection of data on APL-2 across a wider range of the adult PNH population and better support subsequent clinical studies.

Section updated: Section 7.1

Revision 2: Clarification with respect to reporting of Adverse Events (AEs) of special interest.

Rationale: The section has been updated to include thrombosis as an AE of special interest and to reflect the fact that these events will be reported promptly and only within 24 hours if they fulfill the SAE criteria.

Section Updated: Section 11.5

AMENDMENT 3

Revision 1: Protocol updated to remove single dosing period for Cohorts 3 and 4.

Rationale:

1. The first in human single dose study in healthy volunteers has been completed and doses up to and including 1440 mg have been tested providing safety and PK data to support moving directly into multiple dosing in this study.
2. Recruitment of patients will be less problematic if the period of single dosing and its associated monitoring is removed as the study duration will be shorter

Sections updated: All relevant sections (including the Study Flow Chart) throughout the protocol (other than stated objectives) have been updated to remove the single dosing period for Cohorts 3 and 4.

Revision 2: Multiple doses for cohorts 3 and 4 will be updated as follows:

	Multiple SC dose (days 29 to 56) Amendment 1	Multiple SC dose (days 1 to 28) Amendment 3
Cohort 1	5 mg APL-2 / day	N/A
Cohort 2	30 mg APL-2 / day	N/A
Cohort 3	90 mg APL-2 / day	**180 mg APL-2 / day**
Cohort 4	180 mg APL-2 / day	**270 mg APL-2 / day**

Rationale: The doses were updated based on emerging safety, pharmacokinetic and pharmacodynamics data from ongoing studies in healthy subjects currently conducted in Australia where multiple doses up to 270 mg/day for 28 days have been administered to healthy volunteers. This data is summarized in section 4.1.2.2.2. Rationale for this change is described in the updated Section 4.2.2 of this document.

Sections Updated: Sections 4.1.2.2.1, 4.1.2.2.2, 4.2.2 and 8.3.2

Revision 3: Prophylactic immunization requirement at screening updated to include N. meningitides type B (in addition to types A, C, W, Y), Pneumococcal conjugate vaccine or Pneumococcal polysaccharide vaccine 23 (PCV13 or PPSV23, respectively) and Haemophilus influenzae Type B (Hib) vaccination within 2 years prior to Day 1 dosing. Boosters for N. meningitides types A, C, W, Y and B (administered as two separate injections) will also be administered during the study.

Rationale: This update provides broader prophylactic coverage against a range of infectious organisms to which subjects might be susceptible to during complement inhibition and allows use of Penicillin V rather than Augmentin (see revision 4 below).

Section updated: Sections 4.3 and 7.11

Revision 4: Prophylactic antibiotics updated to include Penicillin V as first line therapy commencing on Day 1 of dosing.

Rationale: The amended immunization program at screening allows the use of penicillin V rather than Augmentin as first line prophylaxis. Penicillin V is generally better tolerated by subjects for long term administration i.e. greater than 7-10 days.

Section updated: Sections 4.3 7.11 and 8.4

Revision 5: Updates to address points that required clarification

1. Updated to include LDH at screening as well as other time points as previously omitted in error
2. Updated to include GGT as part of clinical chemistry testing as previously omitted in error.
3. Blood volume table updated to show blood volumes relating to updated protocol i.e. removal of single dosing period

Rationale: Editorial updates required for consistency and clarification

Section updated: Various throughout the document

Revision 6: Drug presentation updated to reflect new doses for Cohorts 3 and 4

Rationale: Increased doses require update to the Study Treatment sections of the protocol to reflect the correct presentation of APL-2

Section updated: Section 8

Revision 7: Statistical Section Updated

Rationale: The Statistical Section of the protocol has been updated to be consistent with the Statistical Analysis Plan (SAP). The SAP provides the detail around the proposed statistical analyses and has also been updated to reflect the protocol amendment. Information that was previously updated within the SAP has either been removed or updated within the body of the protocol to ensure consistency between documents.

Section updated: Section 12

AMENDMENT 4

Background:

Since the initiation of this study, emerging data from this and other clinical studies has become available providing additional evidence of pharmacological activity of APL-2 at doses ≥ 180 mg/day.

In a multiple dose healthy volunteer study (APL-CP1014) a significant decrease in complement mediated hemolytic activity was observed in all APL-2 treated subjects dose levels of 180 and 270 mg/d. The inhibition of hemolytic activity observed at 180 mg/d was partial in all subjects but was essentially complete in 3 out of 4 subjects at 270 mg/d

In this study (APL-CP0514) two subjects have completed cohort 3 dosing receiving a dose of 180 mg/d for 28 days. Both subjects showed clinical improvements, consistent with related changes in blood biomarkers. PPD

In a study in PNH patients who are not receiving eculizumab (PADDOCK), two subjects have received APL-2 doses of 180 mg/d for 28 days. PPD

These initial data suggest that daily SC administration of APL-2 at doses of 180 mg/d or higher can provide sustained inhibition of hemolytic activity in PNH patients. APL-2 may, therefore, provide clinical benefit to subjects with PNH who have not received eculizumab treatment or have a suboptimal response to eculizumab treatment.

Longer term APL-2 dosing and increased subject numbers are required to obtain additional safety and evidence of activity data to support the design Phase II/III studies.

Administration of APL-2 at the proposed dose for Cohort 4 (270 mg/d) is expected to result in APL-2 exposure in subjects (C_{max} and AUC) lower than what has been deemed safe for up to 3 months of SC administration in monkeys. In clinical studies, the same dose has already been shown to be well-tolerated for 28 days in a healthy volunteer study. Based on this data we

propose to extend administration of APL-2 to subjects in Cohort 4 for up to 84 days (12 weeks) if clinical benefits of the treatment can be established within the first 28 days of dosing.

Revision 1:

Increase number of subjects in Cohort 4 to at least N=6 to complete 28 days of dosing.

Rationale:

To obtain additional safety data and evidence of activity at a pharmacological dose.

Sections updated: Synopsis and Sections 6 and 7.

Revision 2:

Allow for dosing period to be extended up to 84 days, contingent on perceived benefits. Subjects in Cohort 4 will receive multiple doses (daily dosing) for 28 days and if, following review of available safety and PD data, subjects have shown evidence of clinical benefits as assessed by the Investigator and Sponsor, they may progress to Part 2 of the study and continue to receive daily doses of APL 2 until Day 84.

Rationale:

To obtain long term safety data and evidence of activity at a pharmacological dose.

Sections updated: Synopsis and Sections 2, 4.3, 6, 9.2 and 9.3

Revision 3: Subjects may participate in more than 1 cohort.

Rationale: The beneficial response was seen in the two subjects who received APL-2 180 mg/d for 28 days may increase at the higher dose of 270 mg/d. Based on the effect observed and the availability of additional toxicology data to support dosing beyond 28 days, participation in more than 1 cohort does not pose additional undue risk and has a reasonable likelihood of providing additional clinical benefits to patient.

Sections updated: Synopsis and Sections 6 and 7

Revision 4: Inclusion Criterion #3: The Body Mass Index criterion has been removed.

Rationale: The weight and BMI restriction has significantly limited the number of patients eligible to participate in this clinical study. Inclusion criterion #3 had already been revised in Amendment 2 (August 12, 2015) based on PK data from ongoing studies at the time. Later, based on the data collected in the healthy volunteer studies, a population PK model was developed to characterize the relationship between APL-2 serum concentrations with dose and time. Using the developed population PK model the possible relationships between PK concentration and subject characteristics such as weight, BMI and gender have been explored. Based on the limited ranges, the impact of weight and BMI on key PK parameters appears to

be small. Amending the inclusion criteria to allow for subjects with higher BMI and/or weight to be enrolled would provide useful information to explore these covariates further.

Sections updated: Synopsis and Section 7.1

Revision 5: Prophylactic immunization requirement for Pneumococcus at screening updated to include a dose of PCV 13 at least 2 weeks prior to Day 1 followed by a dose of PPSV23 at least 8 weeks later.

Rationale: This update follows the Center for Disease Control and Prevention's (CDC) recommendations for Pneumococcal vaccine in patients with immunocompromissing conditions.

Section updated: Sections 2, 4.3 and 8.4 (new section 8.4.1)

Additional Revisions: Editorial changes have been made throughout the protocol for clarity or corrections.

AMENDMENT 5

Background:

On September 29, 2016, the SMC met to review all available safety data and make a decision on extension of dosing for subjects in Cohort 4. At that time, Cohorts 1, 2, and 3 had completed and six subjects had been enrolled into Cohort 4 (3 subjects receiving ongoing treatment with APL-2 and 3 subjects scheduled to commence treatment during the month of October 2016). Subjects enrolled into Cohorts 3 (180 mg/day) and 4 (270 mg/day) have experienced clinical benefit from daily APL-2 treatment.

As of September 29, 2016, the first three subjects in Cohort 4 (PPD) had completed Part 1 and moved into Part 2 and had received treatment with APL-2 270 mg for 51, 30, and 38 days, respectively. There were a total of three AEs that the investigators assigned as possibly related to APL-2 treatment: fatigue, myalgia (30 mg APL-2) and brittle nails (180 mg APL-2). The SMC voted unanimously to extend the duration of APL-2 administration beyond 84 days for subjects in Cohort 4 who experience clinical benefit as evidenced by reduction in LD, increase in Type III CD59 negative RBCs, reduction in blood transfusion requirement, reduction in reticulocytes, and/or patient's perceived improvement in PNH symptoms.

Revision 1: Subjects experiencing clinical benefit during the Part 2A treatment period (Day 29 to Day 84), may enter the Part 2B treatment period (Day 85 to Day 364).

Rationale: If a subject experiences a measureable improvement in PNH symptoms during APL-2 treatment, it would be in the subject's best interest to continue to receive APL-2 treatment for as long as the improvement in symptoms continues. Therefore, in the event that the Investigator deems that a subject experienced clinical benefit during Part 2A, the subject will be invited to participate in Part 2B, and after providing informed consent, will continue to receive ongoing daily APL-2 administration for up to Day 364. In the event that the Investigator deems that a subject did not experience adequate clinical benefit during Part 2A (or at any time during Part 2B), the subject will discontinue daily APL-2 administration and will enter the Part 3 follow-up period.

Sections updated: Synopsis and Sections 2, 4.1.2.1.3, added 4.1.2.2.3, 4.2.2, 4.3, 5.2, 6, 8.3.1.2, 8.3.2, 8.3.3, 9.2, 9.2.1, 9.2.1.1, 9.2.1.2, 9.2.2, 9.2.4, 9.3, 10.1.5, 10.1.7, 10.4, 10.5, 12.10, 12.12, 12.12.1, and removed 12.12.2.

Additional Revisions: Editorial changes have been made throughout the protocol for clarity or corrections.

AMENDMENT 6

Background:

Cohorts 1, 2, and 3 have completed and six subjects have been enrolled into Cohort 4. All 6 subjects have completed at least 28 days dosing with SC APL-2 270 mg/d.

Subjects enrolled into Cohort 3 (180 mg/day) and Cohort 4 (270 mg/day) experienced clinical benefit from daily APL-2 treatment as evidenced by a reduction in LDH, an increase in Hb, an increase in Type III CD59 negative RBCs, and a reduction in reticulocytes. PPD

In addition, the 9-month toxicology study in cynomologous monkeys has been completed and final data from the 3-month interim necropsy and draft data from the final 9-month necropsy are available. The 6-month chronic dosing study in rabbits has also been completed and final data are available. The toxicological findings in the chronic studies were comparable to those observed in the original 28 day IND study and it was concluded that 7 mg/kg/day remains a NOAEL. These pre-clinical observations support chronic administration of 360 mg APL-2/day in humans.

As the study has recently been extended to allow dosing with APL-2 for up to one year it is recognized that the requirement for research nurses to visit the subjects and administer the APL-2 solution using hand-held syringes is inconvenient, and that repeated SC injections may cause pain at the injection site. An ambulatory syringe pump (e.g. Crono Super PID), will be introduced to allow self administration of APL-2 by the subject. A new formulation of APL-2 solution for SC injection in which the diluent is acetate-buffered mannitol rather than dextrose has been developed. This formulation allows storage at 2-8° C making it more suitable for use in an ambulatory setting. Relevant compatibility testing has been performed with the pump evaluating both the 5% dextrose and acetate-buffered mannitol formulations. When the infusion pump is introduced the subjects will receive thorough training by research nurses and/or investigator site staff. Once patients are competent and confident, they will will be able to self-administer APL-2 via the pump.

Revision 1: The protocol is updated to allow intra-subject dose escalation up to 360 mg/day

Rationale: If a subject has demonstrated acceptable tolerability but sub-optimal haematological responses to daily treatment with 270 mg APL-2, the investigator, in conjunction with the sponsor, will be able to increase the daily dose of APL-2 up to 360 mg for that subject in order to improve the clinical outcome.

Revision 2: Updated to include an ambulatory syringe pump for delivery of APL-2 and the new formulation of APL-2 for SC injection

Rationale: It is inconvenient for APL-2 to be administered by a research nurse on a daily basis and hand-held syringes may cause more injection site pain than syringe infusion pumps.

Sections Updated: Synopsis and Sections 2, 4.1.2, 4.1.2.1.3, 4.2.2, 4.3, 8.3.1.1, 8.3.1.2, 8.3.2, 8.3.3, 10.4

AMENDMENT 7

Background:

All 6 subjects in Cohort 4 continued into Part 2B of the study and 5/6 are currently receiving SC APL-2 270 mg/d and continue to experience clinical benefit from daily APL-2 treatment. Therefore, it is proposed that study treatment with APL-2 be further extended to 729 days.

Revision 1: Subjects who continue to experience clinical benefit during the Part 2B treatment period (Day 85 to Day 364), may enter the Part 2C treatment period (Day 365 to Day 729), which follows a less frequest visit schedule.

Rationale: If a subject continues to experience improvement in PNH symptoms during APL-2 treatment, it would be in the subject's best interest to continue to receive APL-2 treatment for as long as the improvement in symptoms continues. Therefore, in the event that the Investigator deems that a subject experienced clinical benefit during Part 2B, the subject will be invited to participate in Part 2C, and after providing informed consent, will continue to receive ongoing daily APL-2 administration for up to Day 729. In the event that the Investigator deems that a subject did not experience adequate clinical benefit during Part 2B, the subject will discontinue daily APL-2 administration and will enter the Part 3 exit period. The visit schedule in Part 2C follows a less frequent schedule based on the safety experience and profile to date.

Section Updated: Synopsis, Section 2, 4.3, 6, 8.3.2, 9.2.1, 9.2.1.1, 9.2.1.2, 9.2.2, 9.2.4, 9.3, 10.1.5, 10.4, 10.5.

Revision 2: Updated to include a new formulation of APL-2 for SC injection.

Rationale: The Sponsor has developed a new formulation of APL-2 solution for SC injection in which the diluent is acetate-buffered sorbitol rather than dextrose. This formulations allows storage at 2-8° C making it more suitable for use in an ambulatory setting. Relevant compatibility testing has been performed with the pump evaluating both the 5% dextrose and acetate-buffered formulations.

Section Updated: Section 4.1.2, 8.3.1.1, and 8.3.1.2

Revision 3: Clarification with respect to reporting of Adverse Events (AEs) of special interest.

Rationale: The section has been updated to include injection site reactions and infusion pump related events as an AE of special interest.

Section Updated: Section 11.5

Additional Revisions: Editorial changes have been made throughout the protocol for clarity or corrections.

2. STUDY FLOW CHART

Study Period	Screen	PART 1 - Multiple Dose (Daily)																											
Study Week	-4	1							2							3							4						
Study Day	-30	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Informed Consent	X																												
Demographics	X																												
Medical, transfusion, and thrombosis history	X																												
Review entry criteria		X																											
Vaccination. A	X																												
Preventive antibiotic. B		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination. C	X																												
12-lead electrocardiogram. D	X	X			X				X							X							X						
APL-2 administration. E		S	S	S	S	H	H	H	S	H	H	H	H	H	H	S	H	H	H	H	H	H	S	H	H	H	H	H	H
Injection site assessment. F		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital sign measurements. G	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X							X							X							X						
Blood. I	X	X	X	X	X				X							X							X						
Pharmacokinetics. **I**		X	X	X	X				X							X							X						
Anti-APL-2 Ab assay		X							X							X							X						
Lactate dehydrogenase	X	X							X							X							X						
Hematology and chemistry.	X	X							X							X							X						
Serology (HIV, HBsAg and HCV). **J**	X																												
Reticulocyte count		X							X							X							X						
Haptoglobin		X							X							X							X						
Coagulation profile		X														X													
Complement profile (C3, CH50 and AH50)		X							X							X							X						
Flow cytometry for PNH		X							X							X							X						
Flow cytometry C3 deposition		X							X							X							X						
Th17/Treg Analysis		X																											
Free hemoglobin		X							X							X							X						
Ferritin, vitamin B12 folate		X							X							X							X						
Pregnancy (B-HCG)	X																												
Urine pregnancy test. K		X							X							X							X						
FACIT fatigue Scale		X														X													
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Thrombosis record (MAVE). L		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

See Study Flow Chart Footnotes below continuation flow chart

Study Period		Part 2A - Treatment (Daily from Day 29 to Day 84)								
	Study Week	5		6	7 and 8		9 and 10		11 and 12	
	Study Day	29	30 to 35	36 to 42	43	44 to 56	57	58 to 70	71	72 to 84
	Study Visit	30	31 to 36	37 to 43	44	45 to 57	58	59 to 71	72	73 to 85
Informed Consent										
Demographics										
Medical, transfusion, and thrombosis history										
Review entry criteria										
Preventive antibiotic. B		X	X	X	X	X	X	X	X	X
Physical examination. C		X					X			
12-lead electrocardiogram. D		X			X		X		X	
APL-2 administration. E		**S**	**H**	**H**	**S**	**H**	**S**	**H**	**S**	**H**
Injection site assessment. F		X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X
Vital sign measurements. G		X	X	X	X	X	X	X	X	X
Urinalysis		X			X		X		X	
Blood. I		X			X		X		X	
Pharmacokinetics. **I**		X			X		X		X	
Anti-APL-2 Ab assay		X							X	
Lactate dehydrogenase		X			X		X		X	
Hematology and chemistry.		X			X		X		X	
Reticulocyte count		X			X		X		X	
Haptoglobin		X			X		X		X	
Coagulation profile		X			X		X		X	
Complement profile (C3, CH50 and AP50)		X			X		X		X	
Flow cytometry for PNH/C3 deposition		X			X		X		X	
Th17/Treg Analysis		X								
Free Hemoglobin		X			X		X		X	
Ferritin, vitamin B12 folate		X			X		X		X	
Urine pregnancy test. K		X			X		X		X	
FACIT fatigue Scale		X			X				X	
Adverse events		X	X	X	X	X	X	X	X	X
Thrombosis record (MAVE) L		X	X	X	X	X	X	X	X	X

See Study Flow Chart Footnotes below continuation flow chart

Study Period		Part 2 B- Treatment (Daily from Day 85 to Day 364) - continued… M											
	Study Week	13 to 16		17 to 20		21 to 24		25 to 28		29 to 32		33 to 36	
	Study Day	85	86 to 112	113	114 to 140	141	142 to 168	169	170 to 196	197	198 to 224	225	226 to 252
	Study Visit	86	87 to 113	114	115 to 141	142	143 to 169	170	171 to 197	198	199 to 225	226	227 to 253
Informed Consent													
Demographics													
Medical, transfusion, and thrombosis history													
Review entry criteria													
Preventive antibiotic. B		X	X	X	X	X	X	X	X	X	X	X	X
Physical examination. C		X											
12-lead electrocardiogram. D		X		X		X		X		X		X	
APL-2 administration. E		**S**	**H**	**S**	**H**	**S**	**H**	**S**	**H**	**S**	**H**	**S**	**H**
Injection site assessment. F		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X
Vital sign measurements. G		X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis		X		X		X		X		X		X	
Blood. I		X		X		X		X		X		X	
Pharmacokinetics. **I**		X		X		X		X		X		X	
Anti-APL-2 Ab assay		X				X				X			
Lactate dehydrogenase		X		X		X		X		X		X	
Hematology and chemistry.		X		X		X		X		X		X	
Coagulation profile		X		X		X		X		X		X	
Reticulocyte count		X		X		X		X		X		X	
Haptoglobin		X		X		X		X		X		X	
Complement profile (C3, CH50 and AP50)		X		X		X		X		X		X	
Flow cytometry for PNH/C3 deposition		X		X		X		X		X		X	
Th17/Treg Analysis		X											
Free Hemoglobin		X		X		X		X		X		X	
Ferritin, vitamin B12 folate		X		X		X		X		X		X	
Urine pregnancy test. K		X		X		X		X		X		X	
FACIT fatigue Scale		X				X				X			
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X
Thrombosis record (MAVE) L		X	X	X	X	X	X	X	X	X	X	X	X

See Study Flow Chart Footnotes below continuation flow chart

	Study Period	… continued - Part 2B - Treatment (Daily from Day 85 to Day 364) M							
	Study Week	37 to 40		41 to 44		45 to 48		49 to 52	
	Study Day	253	254 to 280	281	282 to 308	309	310 to 336	337	338 to 364
	Study Visit	254	255 to 281	282	283 to 309	310	311 to 337	338	339 to 365
Informed Consent									
Demographics									
Medical, transfusion, and thrombosis history									
Review entry criteria									
Preventive antibiotic. B		X	X	X	X	X	X	X	X
Physical examination. C		X							
12-lead electrocardiogram. D		X		X		X		X	
APL-2 administration. E		**S**	**H**	**S**	**H**	**S**	**H**	**S**	**H**
Injection site assessment. F		X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X
Vital sign measurements. G		X	X	X	X	X	X	X	X
Urinalysis		X		X		X		X	
Blood. I		X		X		X		X	
Pharmacokinetics. **I**		X		X		X		X	
Anti-APL-2 Ab assay		X				X			
Lactate dehydrogenase		X		X		X		X	
Hematology and chemistry.		X		X		X		X	
Coagulation profile		X		X		X		X	
Reticulocyte count		X		X		X		X	
Haptoglobin		X		X		X		X	
Complement profile (C3, CH50 and AP50)		X		X		X		X	
Flow cytometry for PNH/C3 deposition		X		X		X		X	
Th17/Treg Analysis		X							
Free Hemoglobin		X		X		X		X	
Ferritin, vitamin B12 folate		X		X		X		X	
Urine pregnancy test. K		X		X		X		X	
FACIT fatigue Scale		X				X			
Adverse events		X	X	X	X	X	X	X	X
Thrombosis record (MAVE) L		X	X	X	X	X	X	X	X

See study flow chart footnotes on next page

Study Period		… continued - Part 2C - Treatment (Daily from Day 365 to Day 729) M						Part 3 – Exit or ET (N)
	Study Week	56	60	68	80	92	104	112
	Study Day	365 (+/-7 days)	421 (+/-7 days)	477 (+/-7 days)	533 (+/-14 days)	617 (+/-14 days)	729 (+/-14 days)	785 (+/-14 days)
	Study Visit	366	367	368	369	370	371	372
Informed Consent								
Demographics								
Medical, transfusion, and thrombosis history								
Review entry criteria								
Preventive antibiotic. B		X	X	X	X	X	X	X
Physical examination. C		X						X
12-lead electrocardiogram. D		X	X	X	X	X	X	X
APL-2 administration. E		**S**	**S**	**S**	**S**	**S**	**S**	
Injection site assessment. F		X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X
Vital sign measurements. G		X	X	X	X	X	X	X
Urinalysis		X	X	X	X	X	X	X
Blood. I		X	X	X	X	X	X	X
Pharmacokinetics. **I**		X	X	X	X	X	X	X
Anti-APL-2 Ab assay		X	X	X	X	X	X	X
Lactate dehydrogenase		X	X	X	X	X	X	X
Hematology and chemistry.		X	X	X	X	X	X	X
Coagulation profile		X	X	X	X	X	X	X
Reticulocyte count		X	X	X	X	X	X	X
Haptoglobin		X	X	X	X	X	X	X
Complement profile (C3, CH50 and AP50)		X	X	X	X	X	X	X
Flow cytometry for PNH/C3 deposition		X	X	X	X	X	X	X
Th17/Treg Analysis		X			X		X	X
Free Hemoglobin		X	X	X	X	X	X	X
Ferritin, vitamin B12 folate		X	X	X	X	X	X	X
Urine pregnancy test. K		X	X	X	X	X	X	X
FACIT fatigue Scale		X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X
Thrombosis record (MAVE) L		X	X	X	X	X	X	X

See study flow chart footnotes on next page

FOOTNOTES:

A. If *Neisseria meningitidis* vaccine/s are administered during screening (up to Day –14), a booster (for both vaccinations) should be administered after 2 months. If Pneumococcal vaccination is required during screening, 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.

B. Preventive antibiotics will be prescribed prior to Visit 2. Antibiotics will be taken from Visit 2 until 14 days after the last dose of APL-2.

C. Full physical examination will be performed at the scheduled time points indicated. A symptom-driven physical examination may be performed at other times, at the PI's discretion.

D. If done on a dosing day, electrocardiograms (ECGs) are to be performed within 30 minutes after dosing.

E. S = Administration at clinical site. H = Administration at subject's home, workplace, or other location convenient to the subject. Treatment may be stopped at any time if the investigator and sponsor conclude that there is no demonstration of clinical benefit to APL-2 continue administration. Subjects may self-administer the SC infusions at home, after receiving appropriate training by a research nurse or other personnel.

F. Injection site assessment will be performed within 30 minutes after APL-2 administration. After the subjects start to self-administer APL-2 via the pump, injection site reactions will no longer be evaluated by research personnel after at-home administrations. Subjects will be instructed to report any injection site reaction to the study coordinator.

G. If done on a dosing day, vital signs will be measured within 2 hours prior to dosing and within 30 minutes after dosing. After the subjects start to self-administer APL-2 via the pump, vital signs will no longer be measured before and after at-home administrations.

H. Reserved – See note E.

I. If done on a dosing day, blood samples will be taken pre-dose with the exception that at Visit 2 only, a pharmacokinetic sample will be taken pre-dose and at 4 hours post-dose.

J. Absence of Human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg), and Hepatitis C virus (HCV), will be confirmed prior to APL-2 administration.

K. If done on a dosing day, urine pregnancy test should be completed for WOCBP prior to dosing.

L. MAVE = Major Adverse Vascular Event. After the subjects start to self-administer APL-2 via the pump, MAVE will no longer be evaluated by research personnel during home visits. Subjects will be instructed to report any events to the study coordinator.

M. If the dose is increased to >270 mg/day, the subject will attend the clinical site for safety visits every 2 weeks (instead of every 4 weeks) for the first 6 weeks after the dose increase i.e. up to an additional 3 clinic visits. The extra clinic visits will be recorded as Unscheduled Visits and will alternate with the scheduled monthly visits.

N. Subjects that discontinue dosing at any time during part 1, 2A, 2B, or 2C will move directly into Part 3 for the exit or early termination visit.

3. ABBREVIATIONS

Abbreviations specific to this study are listed. Pharmacokinetic (PK) parameter abbreviations and definitions may be found in Section 12.9.

ADL	Activities of daily living
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BMI	Body mass index
BUN	Blood urea nitrogen
°C	Degrees Celsius
Chem	Chemistry
CFR	Code of Federal Regulations
CK	Creatine kinase
CRF	Case report form
CS	Clinically significant abnormality
ECG	Electrocardiogram
°F	Degrees Fahrenheit
FDA	Unites States Foods and Drug Administration
FU	Follow-up
g	Gram(s)
GGT	Gamma glutamyl transferase
GCP	Good clinical practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HED	Human equivalent dose
Hem	Hematology
hERG	Human ether-à-go-go-related gene
HIV	Human immunodeficiency virus
HSA	Human serum albumin
IB	Investigator's brochure

ICH	International Conference on Harmonization
kg	Kilogram(s)
L	Liter(s)
LDH	Lactate dehydrogenase
MAC	Membrane attack complex
MAVE	Major Adverse Vascular Event
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mL	Milliliter(s)
µM	Micromolar; micromoles/L
NCS	Not clinically significant
NOEL	No observed effect level
NOAEL	No observed adverse effect level
PD	Pharmacodynamic(s)
PEG	Polyethylene glycol
PEG40	Polyethylene glycol (40 kDa nominal molecular weight)
PI	Principal Investigator or designee
PK	Pharmacokinetic(s)
PT	Prothrombin time
PNH	Paroxysmal nocturnal hemoglobinuria
QTc	Corrected QT interval
QTcB	Bazett's correction
RBC	Red blood cell
SAE	Serious adverse event
SC	Subcutaneous
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOP	Standard operating procedure
$T_{½}$	Serum half-life
TEAE	Treatment-emergent adverse event
UA	Urinalysis
US	Unites States of America
WBC	White blood cell
WHO	World Health Organization
WOCBP	Woman of Child-Bearing Potential

4. INTRODUCTION

4.1 Background

This study is being conducted as the first in a series of studies for the clinical development of APL-2. The trial 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) under standard of care.

4.1.1 Paroxysmal Nocturnal Hemoglobinuria

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

The approval of eculizumab, a monoclonal anti-C5 antibody inhibiting the formation of the MAC, as an effective treatment for PNH, has confirmed that inhibition of the complement cascade is a valid therapeutic strategy for addressing this serious condition. Any therapy that effectively inhibits MAC formation is anticipated to be a plausible candidate treatment for PNH. However, inhibition of MAC formation does not appear to be sufficient to fully control the disease, as many PNH patients receiving eculizumab treatments still suffer from anemia, with only roughly 13% of patients being classified as complete responders, i.e., achieving transfusion independence and normal hemoglobin levels. Most of the patients (53%) were classified as partial responders with decreased transfusion and lactate dehydrogenase, 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. 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.

An overview of available information regarding APL-2 follows below. Details can be found in the APL-2 Investigator's Brochure (Apellis Pharmaceuticals, 2016).

4.1.2 APL-2

APL-2 (PEGylated peptide) is a small 13-amino acid cyclic peptide with 12 natural amino acids and a single synthetic amino acid (methyltryptophan) covalently coupled via a linker to each end of a linear 40kDa polyethylene glycol (PEG40) 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, acetate-buffered mannitol or acetate-buffered sorbitol for administration by subcutaneous injection (SC). APL-2 is being developed for the treatment of paroxysmal nocturnal hemoglobinuria (PNH).

4.1.2.1 Nonclinical Data

4.1.2.1.1 Pharmacology

Primary pharmacology studies were performed with APL-2. *Ex vivo* studies conducted with blood from PNH patients revealed that APL-2 can protect PNH red blood cells (RBCs) from complement-mediated lysis and also prevents RBC opsonization by C3 fragments (i.e., C3 loading). The studies combined a modified Ham's test with flow cytometry. Blood from PNH patients was acidified in the presence of magnesium in order to activate the alternative complement pathway and lyse the PNH erythrocytes. The cells were incubated in the presence of magnesium only (negative control), eculizumab (an anti-C5 antibody approved to treat PNH and used as a positive control / comparator) or APL-2. The surviving erythrocytes, including normal and PNH RBCs, were then labeled with anti-CD59 and anti-C3d and analyzed using standard flow cytometry to assess protection against hemolysis. APL-2 was as effective as eculizumab in protecting PNH RBCs against direct MAC-mediated hemolysis, and, unlike eculizumab, it was also effective in preventing massive opsonization of those cells by C3 fragments. The efficacious dose for humans has been estimated to be between 0.5 mg/kg/d and 1.5 mg/kg/d.

During safety pharmacology studies, APL-2 produced little or no reduction in hERG current amplitude when tested in vitro over a concentration range of 1 µM up to 300 µM in the presence or absence of HSA. APL-2 had no effects on body temperature nor on respiratory and cardiovascular parameters when administered to telemeterized Cynomolgus monkeys at doses of 28 or 140 mg/kg.

4.1.2.1.2 Pharmacokinetics

Pharmacokinetic and toxicokinetics have been performed in rabbits and monkeys administered the drug by IV or SC routes. Excellent bioavailability (approximately 85%) and t½s in the range of 6 to 8 days were obtained with both routes of administration in Cynomolgus monkeys. T½s in rabbits were shorter, ranging from 2 to 3 days.

4.1.2.1.3 Toxicology

To date, Apellis has conducted hERG channel potassium studies; in vivo assessments of cardiovascular and respiratory function in monkeys; pilot 7 day studies in rabbits and monkeys; and 28-day repeat-dose toxicity studies in rabbits and monkeys. A 9-month chronic dosing study has recently completed its *in life* phase and final data from a 3-month interim necropsy and draft data from the 9-month necroscopy are available. A 6-month chronic dosing study in rabbits has been completed and final data are available.

In addition, *in vitro* and *in vivo* assessments of genotoxicity have been performed. In all studies, a group dosed with polyethylene glycol (PEG) with a molecular weight of 40 kDa (PEG40) was included to assess the differences between the PEG moiety of APL-2 and the full drug molecule, APL-2.

APL-2 produced little or no reduction in hERG current amplitude when tested in vitro over a concentration range of 1 µM up to 300 µM in the presence or absence of HSA. APL-2 had no effects on body temperature nor on respiratory and cardiovascular parameters when administered to telemeterized cynomolgus monkeys at doses of 28 or 140 mg/kg.

Pharmacokinetic and toxicokinetics have been performed in rabbits and monkeys administered the drug by IV or SC routes. Excellent SC bioavailability (approximately 85%) was obtained in cynomolgus monkeys. No sex-related differences were noted in either species. Serum concentrations were generally higher on Day 8 or Day 28 compared to Day 1; however, at higher doses of APL-2 serum concentrations were not linear with dose. Mean Cmax was 2890 µg/mL on Day 28 and the $AUC_{(0\text{-}24h)}$ was 66250 µg•hr/mL in rabbits for the 140 mg/kg/d animals. In monkeys, the mean Cmax was 4175 µg/mL on Day 28 and the $AUC_{(0\text{-}24h)}$ was 94400 µg•hr/mL for the 140 mg/kg/d animals. In the 28-day studies the estimated t½ was approximately 2.48 to 2.78 and 6.29 to 8.25 days in rabbits and monkeys, respectively.

APL-2 and PEG40 were well tolerated when administered subcutaneously to rabbits for 7 consecutive days at doses of 20 mg/kg/d or 16 mg/kg/d (for APL-2 and PEG40 respectively) in 5% dextrose. There was no mortality noted and no effects on body weights, food consumption or injection site reactions. At termination, there were neither macro- nor microscopic changes attributable to administration of APL-2 or PEG40. Not surprisingly, APL-2 and PEG40 were mildly antigenic; however, the response did not affect serum concentrations of APL-2. Serum concentrations of APL-2 increased with each dose during the study period.

APL-2 and PEG40 were well tolerated when administered subcutaneously to cynomolgus monkeys for 7 consecutive days at doses of 20 mg/kg/d or 16 mg/kg/d (for APL-2 and PEG40 respectively) in 5% dextrose. A dose of 16 mg/kg/d of PEG40 was chosen as an approximation of the equivalent amount of PEG40 in a dose of 20 mg/kg/d of APL-2. There was no mortality noted and no effects on body weights, food consumption or injection site reactions. At termination there were neither macro- nor microscopic changes attributable to administration of APL-2 or PEG40. There was no evidence of an immunologic response to either molecule. Daily serum concentrations of APL-2 increased during the treatment period, with the maximum concentration noted on Day 6 or 8 for the two animals.

In a 28-day GLP rabbit study with daily SC administration no drug-related in-life findings (clinical signs, body weight, food consumption, ophthalmology) were observed at APL-2 dose levels of 7, 28 or 140 mg/kg/d. APL-2 was well tolerated in the rabbit, with no mortality observed. APL-2 was shown to be weakly immunogenic at all dose levels, but PEG40 (112 mg/kg/d) was also moderately immunogenic, and thus the results observed in APL-2-dosed animals were attributed to the PEG40 portion of the APL-2 molecule and not the peptide moieties. Drug-related dose response increases in red blood cell parameters (RBCs, hematocrit, and hemoglobin) and reticulocyte counts were observed at the 28 and 140 mg/kg/d dose levels, and some, but not all parameters were resolved by the end of the 4 week Recovery Phase of the study. Drug-related minimal kidney tubular degeneration was observed in 2/12 animals dosed with 140 mg/kg/d, and drug-related inflammatory infiltrates at the sites of injection were

observed in the 140 mg/kg/d group. The incidence and severity of this change appeared to be greater in APL-2-dosed animals than in the PEG40 group, although both groups showed a similar inflammatory reaction.

One histopathologic finding induced by PEG40 and not reversible by the end of the 4 week Recovery Phase was macrophage vacuolation in numerous tissues (epithelium of the choroid plexus in the brain, synovium of the femur, bone marrow (sternum and femur), cervix, ovary, ciliary body of the eye, adrenal gland, pituitary gland, salivary gland, kidney, spleen, liver sinusoids, mandibular and/or mesenteric lymph nodes, pancreas, skin (inguinal), stomach, thymus and/or uterus) in both PEG40-treated animals and at all APL-2 dose levels. This finding is a known adaptive change to PEG and was observed in a dose-response fashion. The degree and incidence observed at the 140 mg/kg/d APL-2 dose level was comparable to that in the PEG40 group. Thus, this adaptive finding was attributed to the PEG40 portion of the APL-2 molecule and not the peptide moieties. PEG administration was associated with decreased WBCs and differential lymphocyte counts in the 28 and 140 mg/kg/d APL-2 groups and in the PEG40-treated group. These changes either resolved or showed a tendency toward reversal during the recovery period. PEG40 also induced increases in partial activated thromboplastin time and a decrease in fibrinogen levels at the 28 and 140 mg/kg/d APL-2 dose levels; both changes were resolved by the end of the 4-week Recovery Phase. A no-toxic-effect dose level of APL-2 was concluded to be 7 mg/kg/d.

APL-2 was well tolerated by monkeys during a 28-day GLP study featuring daily SC administration of APL-2 (0, 7, 28 or 140 mg/kg/d) or PEG40 (112 mg/kg/d). All regimens were without effects on in-life parameters, which included mortality, clinical signs, body weight and food consumption, clinical pathology, ophthalmology, antigenicity evaluation, and electrocardiographic evaluations. No treatment-related findings were observed in organ weights or gross necropsy in PEG40-treated animals or in any APL-2 dose level. Histopathological changes consisting of renal tubular degeneration and tubule vacuolation were observed in animals administered either 28 or 140 mg/kg/d. These kidney changes did not resolve during the 4-week Recovery Phase. Inflammatory cell infiltrates at sites of injection were observed for all groups placed on study; however, high-dose animals exhibited a greater severity of infiltrates which were comprised of lymphocytes, plasma cells or granulocytes, as well as frequent multinucleated cells, which appeared to be slightly more pronounced compared to the PEG40 control group.

PEG40 also induced macrophage vacuolation in the monkey similar to that seen in the rabbit, in similar tissues (choroid plexus of the brain (epithelium), bone marrow, adrenal gland, liver sinusoids, mandibular and/or mesenteric lymph nodes, ovary, pituitary, spleen (red pulp), stomach, and/or urinary bladder). An APL-2 dose-response relationship was observed, and the effects in the 140 mg/kg/d group were comparable in severity and incidence to those observed in the PEG40-treated animals. These changes were concluded to be related to the PEG40 portion of the APL-2 molecule and not the peptide moieties. A no-toxic-effect dose level of APL-2 was concluded to be 7 mg/kg/d.

Neither APL-2 nor PEG40 induced genotoxicity under the conditions tested. Both agents were negative in a bacterial reverse-mutation assay (Ames test) with and without S9 metabolic activation, and also negative for the induction of micronuclei in both non-activated and S9-activated test systems in the *in vitro* mammalian cell micronucleus test using TK6 cells

(proficient p53 human lymphocytes). During *in vivo* assessments, APL-2 and PEG40 exhibited no clastogenic effect in the mouse micronucleus model.

In summary, APL-2 had no effects on cardiovascular parameters or hERG channel assays and was not genotoxic *in vitro* and *in vivo*. In general, APL-2 was well tolerated in rabbits and monkeys. APL-2 was slightly to mildly antigenic in the rabbit, but had no observed immunologic effects in monkeys. A number of findings observed in the repeated dose toxicology studies are noted to be associated with high doses of PEGylated proteins and their clearance from the tissues and the body. After 28 days of administration, the primary finding for both APL-2 and PEG40 was macrophage vacuolation in various tissues and kidney tubular degeneration. Administration of PEGylated compounds has been associated with macrophage vacuolation in animals and is associated with the clearance of large molecules from the tissues. Although noted in animal species, the macrophage vacuolation has not been associated with either behavioral or clinical effects in animals nor with any serious adverse events in humans at this time (Ivens, 2013). Furthermore, target organ toxicity in the kidneys has also been associated with administration of PEG in animals (Rudmann, 2013). The majority of the toxicological observations noted in the APL-2 groups were comparable to those noted in the groups of animals receiving PEG40; thus in general, the peptide did not exacerbate the findings attributable to PEG40.

The draft toxicological data, including full histopathological assessment, after 9 months of daily SC administration in the cynomologous monkey and the final toxicological data after 6 months of daily SC administration in the New Zealand white rabbit, were comparable to those observed after 28 days of dosing at the same dose. Doses of 1, 7, and 28 mg/kg/d were investigated. There were no deaths, injection site reactions, ocular effects, gross findings, or changes in organ weight or clinical chemistry parameters.

Mirroring what was observed after 28 days of dosing in monkeys, multi-tissue macrophage vacuolation was observed at ≥7 mg/kg/d (a non-adverse observation) and kidney tubular degeneration was observed in animals at 28 mg/kg/d (an adverse reaction). Based on the draft data, 7 mg/kg/d is still concluded to be a NOAEL in monkeys after considering the toxicological data from the 9 month necropsy in the chronic study. Mirroring what was observed after 28 days of dosing in rabbits, multi-tissue macrophage vacuolation was observed at ≥7 mg/kg/d (a non-adverse observation). Based on the draft data >28 mg/kg/d is still concluded to be a NOAEL in rabbits after considering the toxicological data from the 6-month interim necropsy in the monkey study. The monkey is to be considered the pivotal species from a pharmacological standpoint (i.e. APL-2 is only active in primates) and a toxicological observation [a kidney adverse event was observed at a lower dose in monkeys (28 mg/kg/d) than rabbits (140 mg/kg/d)] that establishes the monkeys as the most sensitive species.

In summary, a number of findings observed in the repeated dose toxicology studies are noted to be associated with high doses of PEGylated proteins and their clearance from the tissues and the body. The primary adverse finding for both APL-2 and PEG40 was macrophage vacuolation in various tissues and kidney tubular degeneration. Administration of PEGylated compounds has been associated with macrophage vacuolation in animals and is associated with the clearance of large molecules from the tissues. Although noted in animal species, the macrophage vacuolation has not been associated with either behavioral or clinical effects in animals nor with any serious adverse events in humans at this time (Ivens, 2013). Furthermore,

target organ toxicity in the kidneys has also been associated with administration of PEG in animals (Rudmann, 2013). Most of the toxicological observations noted in the groups of animals that received APL-2 were comparable to those noted in the groups of animals that received PEG40; thus in general, the peptide did not exacerbate the findings attributable to PEG40.

Collectively there were no findings observed during any of the nonclinical studies, that would preclude testing chronic daily SC administration of APL-2 in humans. Results from the nonclinical APL-2 toxicology program provide good assurance of the safety of the proposed doses of APL-2 in humans by the SC route of administration.

4.1.2.2 Clinical Data

APL-2 SC injection has been tested in two healthy volunteer studies to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of APL-2. Both studies have been completed. The first study was a single ascending dose study (Study APL-CP0713-1) and the second a multiple ascending dose study (Study APL-CP1014).

APL-2 SC administration is also currently being tested in two studies to assess the safety and activity of APL-2 in patients with PNH, including this study (APL-CP0514) and a study in patients who have not received prior treatment with eculizumab (APL-CP-PNH-204).

4.1.2.2.1 Single Ascending Dose Study APL-CP0713-1

Single SC doses of APL-2 or placebo (5% dextrose solution) have been administered to 6 cohorts of healthy volunteers. The first cohort was initiated with a sentinel group of 2 subjects (1 active and 1 placebo) who were dosed 24 hours before the remaining 4 subjects (3 active and 1 placebo); remaining cohorts included 5 subjects (4 active and 1 placebo). Available safety, PK and PD data up to Day 28 were reviewed for each cohort before dosing of the next cohort was initiated. Single doses of 45, 90, 180, 360, 720 mg and 1,440 mg have been studied.

A total of 24 subjects received single SC doses of APL-2 and 7 subjects received placebo. Single dose administration of APL-2 at doses up to 1,440 mg was well tolerated and no serious AEs were reported. The most commonly reported treatment related AEs were headache (5/24 subjects) and redness, itchiness, and/or bruising at the injection site (7/24 subjects). All treatment related AEs were reported as either mild or moderate in severity. There was no consistent onset time of the AEs in relation to the timing of the administration and no apparent dose relationship with the events being reported sporadically across the doses studied. There were no treatment emergent, treatment related AEs reported in subjects who received the highest dose of 1440 mg. All AEs resolved with no sequelae. No safety signals of clinical relevance were observed on review of laboratory data, vital signs, physical examinations or electrocardiogram results following APL-2 administration.

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. After T_{max}, serum APL-2 concentration declined in a steady mono-exponential manner with the rate of decay similar across all dose groups. Exposure ($AUC_{0\text{-}inf}$ and C_{max}) increased monotonically with dose, with the power model indicating dose proportionality. The estimated $t_{½}$ was approximately between 8 and 10 days. PK data is presented in Table 1 below.

PD parameters (CH50, AP50 and complement C3 levels were measured for all cohorts, and intact C3 and iC3b levels were added as additional PD parameters for Cohort 6) were assessed during the study. No significant change in CH50 (classical complement hemolytic activity) was measured at any dose, however, a significant decrease in AP50 (alternative complement hemolytic activity) was measured for Cohort 6. Additionally, a significant and dose-dependent increase in C3 levels was observed, suggesting interaction between APL-2 and its biological target, C3, as expected. Intact C3 and iC3b levels were also increased in the only cohort where it was measured (Cohort 6). Serum C3 level increase ranged from no significant changes at the lowest dose (45 mg) up to an increase of approximately 100% at a dose of 1,440 mg when compared to levels measured in placebo subjects. Maximal levels of C3 were measured approximately 8 to 11 days after a single dose of APL-2, after which levels decreased back towards baseline. This increase in C3 was not correlated with any increase in complement activity as measured by either CH50 or AP50, nor with any other clinical observations.

4.1.2.2.2 Multiple Ascending Dose Study APL-CP1014

In this study, a daily SC dose of APL-2 or placebo (5% dextrose solution) was administered to healthy volunteers for 28 consecutive days. This multiple dose escalation study is completed and final data is available. Cohorts 1 to 4 received 30 mg/d, 90 mg/d , 180 mg/d and 270 mg/d, respectively. The safety monitoring committee (SMC) reviewed safety and tolerability data prior to dose escalation throughout the study.

In total 16 subjects (4 in each Cohort) received SC administration of APL-2 for 28 days and 4 subjects (1 in each Cohort) received placebo. Multiple dose administration of APL-2 at doses up to 270 mg/d for 28 days appeared to be safe well tolerated and no serious AEs were reported. The most commonly reported AEs were headache and URTI. Headache was reported in 4/16 subjects administered APL-2 and two of four subjects administered placebo. In the subjects who received APL-2, three subjects reported treatment-related headaches (one in 30 mg group, two in 270 mg group). In total there were four reports of moderate headache reported in the study and two of these were reported in the APL-2 270 mg group and two in the placebo group. Four of 16 subjects administered APL-2 reported URTI, none of which was considered to be treatment-related. Injection site reactions, reported as pain, pruritus, erythema, bruising and swelling, occurred in three of four subjects who received the highest dose (270 mg daily for 28 days) of APL-2. The injection site reactions were mild in severity and sporadic in nature, i.e. not reported at every injection, and none were considered, by the investigator to be clinically significant. PPD [redacted] No other safety signals of clinical relevance were observed on review of laboratory data, vital signs, physical examinations or electrocardiogram results following APL-2 administration.

After first dose, APL-2 was slowly absorbed into the systemic circulation with a median T_{max} of 24 hours across all dose groups indicating that the dose was still being absorbed into the systemic circulation at the time of next dose. Median serum concentration increased with each repeat dose, with concentrations close to steady state by Day 22. After Day 29, serum APL-2 concentration declined in a steady mono-exponential manner with the rate of decay similar

across all dose groups. Exposure (AUC_{tau} and C_{max}) increased monotonically with dose at both Day 1 and Day 28, indicating dose proportionality. PK data is presented in Table 1 below.

As with the single dose Phase I study APL-CP0713-1, a dose-dependent increase in C3 levels was observed. Additionally, a statistically significant decrease in the alternative pathway of complement activity (i.e. as measured by AP50 assay) was observed at doses of 30, 180 and 270 mg/d. The lowest AP50 values were recorded on Day 29 in the 270 mg/d group and the mean percentage reduction from baseline was -77%. Reductions began to resolve on cessation of dosing with APL-2. C3a, C5a, intact C3 and iC3b were assessed in the 180 and 270 mg groups and reductions in C3a, C5a and increase in iC3b were observed during the dosing period at both dose levels. Taken as a whole, these PD observations are consistent with a conclusion that APL-2 is interacting with complement C3 and inhibiting its activation through the alternative pathway.

4.1.2.2.3 APL-2 in eculizumab-naïve patients with PNH

This study is an ongoing initial exploration of APL-2 in patients with PNH who have not received prior treatment with eculizumab. The study is comprised of two cohorts with three subjects per cohort, and to date, Cohort 1 has been completed and Cohort 2 is ongoing. To date treatment with APL-2 270 mg/day has been well-tolerated for at least three months and has provided clinical benefit in subjects with PNH. Based on the emerging data, dosing will continue for up to 364 days.

4.2 Rationale

4.2.1 Purpose of the Study

This study will be the initial exploration of APL-2 in patients with PNH. The assessments of the safety, tolerability, PK, and PD following administration of single and multiples doses of APL-2 will guide decisions to further develop the drug.

4.2.2 Dose Selection

APL-2 appeared well tolerated in a panel of standard animal toxicology studies and initial clinical testing in healthy volunteers. Predicted C_{max} and AUC values derived from a population-based PK model built from available single-dose and repeated-dose clinical data. Monkey and human PK data were used to compare APL-2 exposures and support dose selection rather than the cruder method of comparing doses based on an mg/m^2 basis (i.e. using a conversion factor of 3.1× to convert rabbit or cynomolgus monkey mg/kg doses into human-equivalent doses [HED]).

In the nonclinical toxicology studies described in the IB, the no observed effect level (NOEL) in both monkeys and rabbits was determined to be >20 mg/kg/d in a 7 day non-GLP study (daily drug administration). A no observed adverse effect level (NOAEL) between 7 mg/kg/day and 28 mg/kg/d in both species was established during a 28-day GLP study (daily drug administration). Monkeys are considered the most relevant and pivotal species since APL-2 is only pharmacologically active as a complement inhibitor in primates. Additionally, PK parameters observed in monkeys (C_{max}, $t_{1/2}$, and AUCs) correlate better with PK data obtained from the clinical studies APL-CP0713-1 and APL-CP1014.

The final human PK data from the studies conducted in healthy volunteers (APL-CP0713-1 and APL-CP1014) were analyzed and compared to the PK data at the NOAEL in cynomolgus monkeys (see Table 1).

Table 1 (updated to include final data from the clinical trials): Comparison of PK parameters obtained from the IND-enabling toxicology study and ongoing clinical trials. All values reported as arithmetic means.

	Notes	Dose (mg/kg)	C_{max} (µg/mL)	C_{max} % NOAEL	$AUC_{0\text{-}29d}$ (µg•h/mL)	$AUC_{0\text{-}29d}$ % NOAEL	$AUC_{0\text{-}\infty}$ (µg•h/mL)
Monkey	NOAEL; Study 13CATX-004	7	931	--	**442,950**	--	**N/A**
Human	45 mg single dose; APL-CP0713-1	0.6[a]	7	1%			**3,190**
	90 mg single dose; APL-CP0713-1	1.3[a]	16	2%			**7,670**
	180 mg single dose; APL-CP0713-1	2.6[a]	29	3%			**15,500**
	360 mg single dose; APL-CP0713-1	5.1[a]	74	8%			**30,000**
	720 mg single dose; APL-CP0713-1	10.3[a]	139	15%			**59,000**
	1440 mg single dose; APL-CP0713-1	20.6[a]	252	27%			**98,000**
	30 mg/d x 28 days; APL-CP1014	0.43[a]	77	8%	**28,000**[b]	6%	**55,900**[b]
	90 mg/d x 28 days; APL-CP1014	1.29[a]	259	28%	**100,900**[b]	23%	**193,200**[b]
	180 mg/d x 28 days; APL-CP1014	2.6[a]	473	51%	**160,000**[b]	36%	**320,400**[b]
	270 mg/d x 28 days; APL-CP1014	3.9[a]	670	72%	**208,500**[b]	47%	414,000[b]
	360 mg/d PREDICTED	5.14	790	85%	**269,400**[b]	61%	**510,500**[b]

[a] Assuming 70 kg subject.
[b] $AUC_{0\text{-}\infty}$ was not calculated. Approximate values reported from $AUC_{0\text{-}29}$ and $AUC_{0\text{-}84}$ (or $AUC_{0\text{-}last}$)

At the time of initiation of the study (when final data was not available), a conservative recommended starting dose, based on predictions from PK modelling was selected– a dose that was expected to result in a C_{max} that is 1/50th the C_{max} observed at the NOAEL dose in monkeys – was 5 mg/d (0.07 mg/kg/d for a 70 kg subject). This dose was expected to result in an AUC exposure that was approximately 90 times lower than the AUC observed at the NOAEL dose in monkeys. This proposed starting dose was particularly conservative because the PK model used was based on data derived in healthy volunteers and the PK behavior of APL-2 might be substantially different in PNH patients. The initial dose provided PK data to confirm the validity of this PK model in PNH patients.

Following review of data from ongoing studies in healthy volunteers the doses proposed for Cohorts 3 and 4 were amended to 180 and 270 mg/d, respectively. A repeated dose of 270 mg/d of APL-2 in humans resulted in a C_{max} of 670 µg/mL and a total exposure ($AUC_{0\text{-}29d}$) of 208,500 µg•h/mL. These C_{max} and AUC values are approximately 72% and 47% of those observed at the NOAEL dose in cynomolgus monkeys. From a pharmacological standpoint, 180 mg/d was also the lowest dose that resulted in pharmacology in humans (as measured by a decrease in AP50). As a safety consideration, only doses that have been previously shown to be well tolerated in healthy volunteers will be tested in this PNH study.

The starting dose for Cohort 4 is 270 mg/d, with the option to increase the dose on an individual subject basis, up to 360 mg/d, which is the dose expected to reach approximately 85% of the Cmax of the NOAEL observed in monkeys. The daily dose will not exceed 360 mg/d without a protocol amendment.

4.3 Risk/Benefit

The safety monitoring practices employed by this protocol (i.e., physical examination, vital signs, 12-lead ECG, hematology, serum chemistry, urinalysis, coagulation, injection site reaction monitoring, and AE questioning) are adequate to protect the subjects' safety.

The approximate volume of blood planned for collection from each subject over the course of the study (see Section 0) has been limited to a maximum of approximately 896 mL over the course of the study, in order to minimize the impact on the overall health of these anemic subjects. If the dose of APL-2 is increased above 270 mg/day, up to three additional blood draws will be scheduled, requiring an additional blood volume of up to 45 mL (up to 687 mL in total).

Systemic complement inhibition might predispose individuals to infections caused by encapsulated organisms, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*. Subjects will be required to provide documented evidence of vaccination against *Neisseria meningitides* types A, C, W, Y and B (administered as two separate vaccinations), *Streptococcus pneumoniae* (Pneumococcal conjugate vaccine or Pneumococcal polysaccharide vaccine 23 [PCV13 or PPSV23, respectively]) and *Haemophilus influenzae* Type B (Hib) within 2 years prior to Day 1 dosing, OR willing to receive appropriate vaccinations at least two weeks prior to dosing on Day 1 and any required booster doses during the study (See Section 8.4.1 for further details). In addition to the vaccinations against these encapsulated organisms, prophylactic antibiotic therapy (penicillin V 500 mg twice a day) will be prescribed to all subjects at the initiation of dosing (Day 1) and continue until two weeks after the last dose to minimize potential infection risk. Body temperature and vital signs will be monitored daily during the dosing portion of the study and relevant blood parameters monitored regularly throughout the study to assess for signs of infection. The principal investigator should be contacted immediately in the event of a suspected infection despite prophylactic antibiotic treatment for guidance and appropriate action to be taken.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on beta-lactam antibiotic (e.g. penicillin, amoxicillin, etc.) therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity. Before initiating therapy with penicillin V, careful inquiry should be made concerning previous hypersensitivity reactions to amoxicillin, penicillins or cephalosporins. Subjects with a known hypersensitivity to penicillin/amoxicillin may be prescribed erythromycin 500 mg twice daily as an alternative treatment at the outset (See Section 8.4.2 for details).

Other frequently reported adverse effects in patients taking penicillin are diarrhea/loose stools, nausea, skin rashes, urticaria and vomiting. Patients should, therefore, be advised that these reactions may occur. Treatment may be switched to erythromycin 500mg twice daily (see Section 8.4.2 for details) if there is evidence of penicillin-related tolerability issue (such as nausea and diarrhea).

As kidneys are believed to be the key target organ for toxicity from prolonged APL-2 high level exposure, renal function will be closely monitored during this APL-2 repeated-dose clinical testing.

There is a potential health benefit for trial participants from receipt of study drug. We propose to administer APL-2 to PNH patients who continue to be anemic despite treatment with eculizumab. If efficacious and safe, APL-2 is expected to improve Hb levels and reduce transfusion dependency in these patients. At the dose level of 270 mg/d of APL-2 a significant decrease in complement mediated hemolytic activity was observed in all APL-2 treated subjects in the healthy volunteer study. APL-2 may, therefore, 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 and 28 days in healthy volunteer studies. Based on this data we propose to administer APL-2 to subjects in Cohort 4 for up to 84 days (12 weeks) in Part 2A and then for up to 52 weeks (Part 2B). If subjects continue to demonstrate benefit, APL-2 will be administered for up to 104 weeks (Part 2C). Subjects will be assessed by the Investigator every month for Part 2A and Part 2B. Subjects will be assessed by the Investigator 4 weeks, 8 weeks, and then every 12 weeks until Day 729. The available safety, PK and PD data will be reviewed by the Investigator and Sponsor on an ongoing basis. If the dose of APL-2 is increased to above 270 mg/day, the subject will be assessed by the investigator every 2 weeks (instead of every month) for the first 6 weeks after the dose increase. APL-2 will only be continued if there is evidence of clinical benefit to the patient, as determined by the Investigator and the Sponsor. An indirect health benefit to the patients enrolled in this trial is the free medical tests received at screening and during the study.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1 Study Objectives

The primary objectives of the study are to assess the safety, tolerability and pharmacokinetics of single and multiple subcutaneous (SC) doses of APL-2 in subjects with paroxysmal nocturnal hemoglobinuria (PNH) who are still anemic after treatment with eculizumab (Soliris®).

An exploratory objective of the study is to assess the pharmacodynamics (PD) of single and multiple SC doses of APL-2 when administered to PNH patients. See "Study Endpoints" in Section 5.2.

5.2 Study Endpoints

The primary endpoints of the study are the number and severity of TEAEs and PK parameters of APL-2 following administration of single and multiple SC doses.

As exploratory PD endpoints, the following markers will be studied:

- Complement (e.g., CH50, AH50, and C3) hemolytic activity and levels
- C3 deposition on RBC cells
- Hemoglobin
- Reticulocytes

- Lactate dehydrogenase (LDH)
- Bilirubin
- Clonal distribution of PNH vs normal bone marrow derived cells
- Th17/Treg analysis
- Red blood cell transfusions

6. STUDY DESIGN

This is a Phase 1, open-label, prospective, non-randomized, single and multiple ascending dose, study in patients with PNH. The study is planned to enroll approximately 15 subjects across 4 cohorts. Cohorts 1-3 will comprise 2 subjects in each cohort. Cohort 4 will enroll sufficient subjects to ensure at least 6 subjects complete 28 days of dosing with APL-2. Subjects may participate in more than one cohort.

Safety will be assessed throughout the study; serial blood samples and urine samples will be collected. Blood samples will also be collected for the PK assessment of APL-2. Additional samples for assessment of PD will also be collected. Interim PK analyses may be performed to reconsider the sampling time points as the study progresses and to guide the dose-escalation decision. Cumulative data will be reviewed by the Safety Monitoring Committee (SMC) on an regular ongoing basis and the frequency of SMC review meetings will be described in the SMC charter (see Section 9.3).

The planned length of participation (from Screening [Visit 1] to completion of the Exit visit) in the study for each subject is approximately 140 days for Cohorts 1 and 2, 115 days for Cohort 3 and up to 785 days for Cohort 4 .

For prior study design including single doses and waiting period (Cohorts 1, 2, and 3), refer to Version 4.0, Amendment 2, 3, and 4 of the protocol.

Subjects in Cohort 4 will initially receive 270 mg SC APL-2 daily for 28 days. Subjects will be entered into the study at Visit 2 (Day 1) at a time designated by the PI and will receive daily SC doses of APL-2 at Visits 2 to 29. The first 4 daily SC doses of APL-2 (Visits 2 to 5) as well as doses at Visits 9, 16 and 23 will be administered at the clinical site. Subjects will remain in the clinic for at least 4 hours after the first dosing at Visit 2. If a subject progresses to Part 2A, doses at Visits 30, 44, 58 and 72 (Days 29, 43, 57 and 71) will be administered at the clinical site, and the subject then progresses to Part 2B, doses at Visit 86, 114, 142, 170, 198, 226, 254, 282, 310, and 338 (Days 85, 113, 141, 169, 197, 225, 253, 281, 309, and 337) will be administered at the clinical site. If a subject progesses to Part 2C, doses at Visits 366, 367, 368, 369, 370 and 371 (Days 365, 421, 477, 533, 617, and 729) will be administered at the clinical site. If a subject has a sub-optimal clinical response during daily dosing with 270 mg APL-2, the dose may be increased up to 360 mg/day, and doses will be administered at the clinical site every 2 weeks for the first 6 weeks after commencing the higher dose. The remaining multiple doses will be administered by a trained nurse at the subject's home, workplace, or other location convenient to the subject. After completion of dosing, subjects will enter the Part 3, and return to the clinical site for exit procedures at Visit 372 Exit Visit (8 weeks after the last dose). See Study Flow Chart in Section 2.

7. SUBJECT SELECTION

The study is planned to enroll approximately 15 subjects across 4 Cohorts. Cohorts 1-3 will comprise 2 subjects in each cohort. Cohort 4 will enroll sufficient subjects to ensure at least 6 subjects complete 28 days of dosing. Subjects may participate in more than one cohort. Additional cohorts may be enrolled if it is deemed appropriate by the Sponsor in consultation with the SMC to repeat a dose level or to study an interim dose level.

7.1 Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study, unless otherwise specified:

1. Male or Female
2. At least 18 years of age
3. Weigh >55 kg
4. Diagnosed with PNH
5. On treatment with eculizumab (Soliris®) for at least 3 months
6. Hb < 10 g/dL at screening **OR** have received at least one transfusion within 12 months prior to screening
7. Platelet count of >30,000/mm^3
8. Absolute neutrophil count >500/mm^3
9. Women of child-bearing potential (WOCBP) must have a negative pregnancy test at screening and must agree to use protocol defined methods of contraception for the duration of the study (see below)
10. Males with female partners of child bearing potential must agree to use protocol defined methods of contraception (see below) and agree to refrain from donating sperm for the duration of the study
11. Willing and able to give informed consent

7.1.1 Approved methods of contraception

Approved methods of contraception include: abstinence, oral contraceptives, intrauterine device, medically acceptable double-barrier methods (diaphragm in combination with spermicidal jelly/foam, condom with spermicidal jelly/foam), implantable or injectable contraceptives (like Norplant or DepoProvera) or removable birth control device (like NuvaRing or Evra patches); and/or surgical sterilization (at least 6 months before dosing). Subjects practicing abstinence and coitus interruptus (pull out method) must agree to use an additional approved method of contraception during the study.

7.2 Exclusion Criteria

Subjects will be excluded from the study if there is evidence of any of the following criteria at screening or before dosing on Visit 2, as appropriate.

1. Active bacterial infection

2. Known infection with hepatitis B, C or HIV
3. Hereditary complement deficiency
4. History of bone marrow transplantation
5. Participation in any other investigational drug trial or exposure to other investigational agent, device or procedure within 30 days
6. Evidence of QTcF prolongation defined as >450 ms for males and >470 ms for females at screening
7. Creatinine clearance (CrCl) <50 mL/min (Cockcroft-Gault formula) at screening
8. Breast-feeding women
9. History of meningococcal disease
10. No vaccination against *N. meningitidis* types A, C, W, Y and B (administered as two separate vaccinations), Pneumococcal conjugate vaccine or Pneumococcal polysaccharide vaccine 23 (PCV13 or PPSV23, respectively) and *Haemophilus influenzae* Type B (Hib) vaccination within 2 years prior to Day 1 (Visit 2) dosing.

8. STUDY TREATMENTS

8.1 Allocation to Treatment

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all eligibility criteria will be scheduled to enter the study and dosed in the next available cohort.

8.2 Blinding

None: This is an open-label study.

8.3 Treatments Administered

Sterile solutions of APL-2, up to 150 mg/mL, administered subcutaneously.

8.3.1 Drug supplies

8.3.1.1 Identity of Investigational Products

APL-2 will be supplied either as: 1) sterile APL-2 solution in 5% dextrose at concentrations of 10, 40, 100 or 150 mg/mL, supplied as 1-mL stoppered glass vials; 2) sterile APL-2 in acetate-buffered mannitol or acetated-buffered sorbitol solution, pH 5.0, at concentrations of up to 60 mg/mL, supplied as 10 mL stoppered glass vials; or 3) sterile vials containing lyophilized APL-2 supplied as stoppered glass vials, to be reconstituted to a concentration of 40 - 150 mg/mL using the 5% dextrose diluent provided by the sponsor. The volume of injection will be adjusted to achieve the desired dose. A separate dosing and administration document will be provided to study staff, providing details of concentrations and volumes for each cohort.

8.3.1.2 Study Supplies

The Sponsor will supply vials of APL-2 in 5% dextrose solution, APL-2 acetate-buffered mannitol solution, APL-2 acetate-buffered sorbitol solution or lyophilized APL-2, and 5% dextrose diluent to the clinical site. The Sponsor will also supply needles, syringes, infusions sets, and infusion pumps (e.g. Crono Super PID) as required. Drug accountability records will be maintained by a pharmacist or other appropriately qualified designated person at the clinical site, and will be made available for review by the Sponsor.

APL-2 in 5% dextrose solution and lyophilized APL-2 should be stored at -20°C, APL-2 acetate-buffered mannitol and acetate-buffered sorbitol solutions should be stored at 2-8°C; and dextrose diluent should be stored at 15-30°C. Access to the drug supplies should be restricted, and the Pharmacist or other appropriately qualified designated person will maintain drug accountability records.

8.3.1.3 Accountability

Records will be made of the receipt and dispensing of the drugs supplied both at the clinical site and by the research nurse.

Subjects will be dispensed investigational product at 4 weekly intervals.

At the conclusion of the study, any unused investigational product will be returned to the Sponsor or designee, or destroyed per Sponsor instructions or the site's SOP. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

8.3.2 Planned Dose Levels

Planned doses will be as follows:

Cohort	Planned dosing schedule (Amendment 7)
1	25 mg on Day 1 then 5 mg/day from Day 29 to Day 56
2	50 mg on Day 1 then 30 mg/day from Day 29 to Day 56
3	180 mg/day from Day 1 to Day 28
4	270 mg/day (up to 360 mg/day) from Day 1 to Day 729* with optional instrasubject escalation up to 360mg/day after Day 28**

*Subjects may initially receive APL-2 for 28 days (Part 1) and if there is evidence of clinical benefit they may continue to receive APL-2 until Day 84 (Part 2A) and if there is ongoing evidence of clinical benefit they may continue to receive APL-2 until Day 364 (Part 2B). If subjects continue to have clinical benefit they may receive APL-2 until Day 729 (Part 2C).

** Individual patient dose escalation up to a dose of 360 mg/day may occur in subjects who have a sub-optimal hematological response but acceptable tolerability.

The self-administration pump can be programmed to deliver in volumes of one mL increments, and no fractions of thereof. As a result, when delivering a dose of 270 mg, a nominal dose of up to 280 mg may be delivered dependent upon the concentration of the formulation (e.g. formulation 40 mg/mL administered in 7mL provides a dose of 280 mg). This difference of approximately 4% is considered an acceptable margin which will have minimal/no impact on the PK/PD or efficacy of APL-2.

8.3.3 Drug Administration

A pharmacist or other appropriately qualified designated person will dispense the vials of APL-2 solution or vials of lyophilized APL-2 and diluent. The dispensing and other APL-2 accountability records will be maintained at the clinic and made available for review by the sponsor. If the dose volume is ≤3 mL, doses will be administered as 1 or 2 bolus SC injections. If the dose volume is >3 mL, doses will be administered as SC infusions. The preferred site of administration is the abdomen; however, if a subject does not tolerate administration into the abdomen alternative sites may be selected e.g. thighs or upper arm.

Research nurses or other appropriately qualified research personnel will administer bolus SC injections. Subjects may self-administer the SC infusions, after receiving appropriate training by a research nurse or other personnel. The injections will be administered 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.

8.3.4 Additional Dose Levels

Repeat of any cohort or the addition of an interim dose level may be added, based on emerging safety, PK and PD data. Any amendments to doses will be made in consultation with and upon recommendation from the SMC. The Institutional Review Board (IRB) will be immediately notified of this revised approach.

8.4 Concomitant Medications

8.4.1 Vaccinations

Subjects will be required to provide documented evidence of having received the following vaccines within 2 years prior to Day 1 dosing.

- *Neisseria meningitides* types A, C, W, Y: Menactra®, Menomune® or Menveo®
- *Neisseria meningitides* type B: Bexsero® or Trumenba®
- *Streptococcus pneumoniae:* Prevnar 13®(PCV13) or Pneumovax® (PPSV23)
- *Haemophilus influenzae* type B: PedvaxHIB®, ActHIB® or Hiberix®

If subjects are not able to provide documented evidence of having received the vaccinations above, they will receive the vaccinations following the CDC's recommendations for vaccination in patients with immunocompromissing conditions as described below (CDC, 2016).

- *Neisseria meningitides* types A, C, W, Y: Menactra®, Menomune® or Menveo®. First dose at least two weeks prior to dosing on Day 1 with a booster after 2 months.
- *Neisseria meningitides* type B: Bexsero® or Trumenba®. First dose at least two weeks prior to dosing on Day 1 with a booster after 2 months.
- *Streptococcus pneumoniae:* Prevnar 13®(PCV13) at least two weeks prior to dosing on Day 1 and Pneumovax® (PPSV23) after 2 months.
- *Haemophilus influenzae* type B: PedvaxHIB®, ActHIB® or Hiberix® at least two weeks prior to dosing on Day 1.

8.4.2 Prophylactic antibiotics

Prophylactic antibiotic therapy will be prescribed to all subjects to minimize potential infection risk. Prophylactic antibiotics will be initiated at Visit 2 before initiation of APL-2 dosing and continue until 2 weeks after the last dose of study medication.

8.4.2.1 Primary prophylactic antibiotic

- Penicillin V 500 mg twice daily

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on beta-lactam antibiotic (e.g. penicillin, amoxicillin, etc.) therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity. Before initiating therapy with penicillin V, careful inquiry should be made concerning previous hypersensitivity reactions to amoxicillin, penicillins or cephalosporins. If subjects have a known hypersensitivity to penicillin/amoxicillin they may be prescribed an alternative antibiotic at the outset.

Other frequently reported adverse effects in patients taking penicillin are diarrhea/loose stools, nausea, skin rashes and urticaria, and vomiting. Patients should, therefore, be advised that these reactions may occur.

8.4.2.2 Alternative prophylactic antibiotics

- Erythromycin 500 mg twice daily

Erythromycin 500 mg twice daily may be considered as a suitable alternative in subjects who are unable to tolerate penicillin.

Treatment should be switched to another alternative antibiotic if there is evidence of penicillin or erythromycin-related tolerability issue (such as nausea and diarrhea). The PI will discuss and agree to a suitable alternative with the sponsor's medical monitor. The agreement will be noted in the subject's medical records.

8.4.2.3 Rescue antibiotics

Body temperature and vital signs will be monitored daily during the dosing portion of the study and relevant blood parameters monitored regularly throughout the study to assess for signs of infection. The principal investigator should be contacted immediately in the event of a suspected infection despite prophylactic antibiotic treatment for guidance and appropriate action to be taken. Action to be taken may include administration of a broad spectrum antibiotic to cover possible resistant organisms such as resistant pneumococcus (e.g. levofloxacin/augmentin).

9. STUDY PROCEDURES

Please see the Study Flow Chart in Section 2 for a summary of the schedule of study participation and procedures.

9.1 Screening (Visit 1)

Screening will begin within 30 days prior to dosing to confirm that subjects meet the subject selection criteria for the study. Informed consent will be obtained at screening (see Section

13.3.3). Subjects will have to meet all eligibility criteria before being enrolled into the study (see Section 7).

The following will be recorded at screening: medical history and demographic data, including, sex, age, race, body weight (kg), height (cm).

Screening procedures are listed in the Study Flow Chart in Section 2.

9.2 Treatment Period (Visits 2 to 36)

For prior study design including dosing schedules for Cohort 1, 2, and 3, refer to Version 4.0, Amendments 2, 3, and 4 of the protocol.

9.2.1 Dosing Period (Visits 2 to 729)

Subjects will receive daily SC doses of APL-2 in the mornings of Visits 2 to 29. Following review of available safety, PK and PD data by the Investigator and Sponsor subjects demonstrating clinical benefit from the treatment may progress to Part 2A of the study and continue to receive daily doses of APL 2 until Visit 85 (Day 84) , then subjects continuing to demonstrate clinical benefit from the treatment may progress to Part 2B of the study and continue to receive daily doses of APL 2 until Visit 365 (Day 364). Subjects continuing to demonstrate clinical benefit may progress to Part 2C of the study and continue to receive daily doses of APL-2 until Visit 371 (Day 729). APL-2 will be administered at the site by study personnel or at the subject's home, workplace, or other location convenient to the subject by a trained research nurse. Subjects may self-administer the SC infusions, after receiving appropriate training by a research nurse or other personnel.

9.2.1.1 Clinical Site Administration (Part 1 Visits 2-5, 9, 16, & 23; Part 2A Visits 30, 44, 58, & 72, and Part 2B Visits 86, 114, 142, 170, 198, 226, 254, 282, 310, 338; Part 2C Visits 366, 367, 368, 369, 370 and 371)

Subjects will receive a daily SC dose of APL-2 starting on Visit 2. See Section 8.3.2.

The first 4 daily SC doses of APL-2 (Visit 2 to 5) as well as doses on Visits 9, 16, 23, 30, 44, 58 and 72 will be administered at the clinical site. Subjects will remain in the clinic at least 4 hours after dosing at Visit 2 only.

Blood samples for PK/PD will be taken at the following time points during Visit 2 to Visit 86 of the study:

- PK + PD: Pre-dose at Visit 2
- PK: 4 hours post-dose at Visit 2
- PK only: Pre-dose at Visits 3, 4 and 5
- PK + PD: Pre-dose at Visits 9, 16, 23, 30, 44, 58 and 72.

Blood samples for PK/PD will be then be taken pre-dose at every subsequent scheduled clinic visit up to and including the Exit Visit.

Additional procedures for each visit are listed in the Study Flow Chart in Section 2.

9.2.1.2 Multiple-Dose Outpatient Administration (Part 1 Visits 6-8, 10-15, 17-22 and 24-29; Part 2A Visits 31-43, 45-57, 59-71, & 73-85, Part 2B Visits 87-113, 115-141, 143-169, 171-197, 199-225, 227-253, 255-281, 283-309, 311-337, and 339-365, Part 2C Visits 366, 367, 368, 369, 370 and 371)

From Visit 6 to Visit 371, with the exception of doses administered at the clinical site as specified above, daily doses of APL-2 will be administered by a trained research nurse, caregiver, or self-administered. These daily doses of APL-2 may be administered at the subject's home, workplace, or other location convenient to the subject.

If a trained research nurse completes APL-2 administration, safety, tolerability and concomitant medication will be monitored. If the subject (or caregiver) self-administers the SC infusions, after receiving appropriate training by a research nurse or other personnel, adverse events and concomitant medications will be reported to the clinic site.

9.2.2 Exit Visit (Visit 372)

All subjects will be asked to return to the clinical site for an Exit Visit 8 weeks following the last administration of APL-2. For any subject enrolled in the study, study participation will be concluded following the Exit visit evaluations (Visit 372) approximately 8 weeks after the last dose of APL-2 or at early termination. Should any subject withdraw or be withdrawn from the study, the Exit visit evaluations should be performed including the collection of blood samples for PK and/or PD assessments, as well as a post-dose antigenicity sample if not yet collected.

Blood samples for PK/PD will be taken at Exit Visit. The Exit visit procedures are listed in the Study Flow Chart in Section 2.

9.2.3 Unscheduled Follow-up Visits

The safety and PK sampling may be extended or modified with additional follow-up visits.

All subjects will be asked to return to the clinical site for additional follow-up visits if considered necessary by the PI, the sponsor or the SMC or if PK/PD sampling schedule is modified or extended based on interim results.

Unscheduled follow-up visits may include any of the procedures listed in the Study Flow Chart in Section 2.

9.2.4 Scheduled End of Study

The end of the study is scheduled after completion of the Exit visit evaluations in the 4 cohorts. This may change in the event that the study is terminated early if dose-limiting clinical safety endpoints have been reached to preclude further increases of dose, additional cohorts are enrolled, additional time is required to review safety data, extended safety and PK sampling is added for a cohort (e.g., extended beyond Visit 372), or a decision is made to complete an unscheduled analysis between cohorts.

9.3 Dose Escalation and Periodic Safety Review

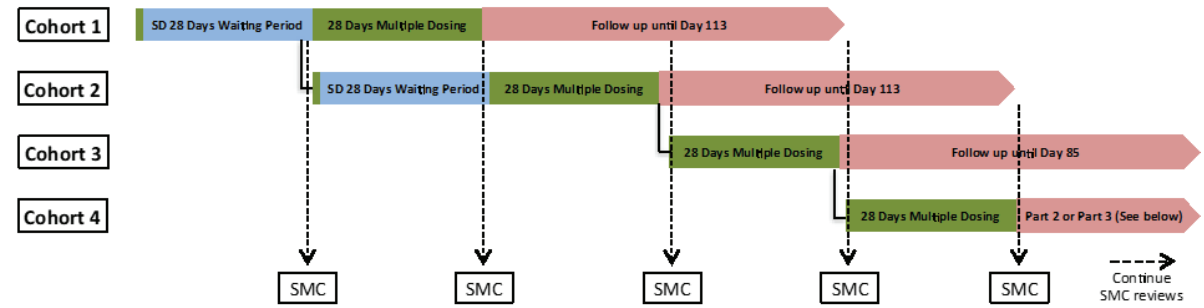
Initiation of the next dose level (i.e. next cohort) will occur as follows:

For Cohorts 1 and 2, subjects will receive a single SC dose of APL-2 on Day 1. At least twenty-eight days after they receive the single injection, subjects will enter the multiple-dose period

and will receive SC APL-2 daily for 28 days at the corresponding multiple dose for their cohort. After both subjects in the preceding cohort have completed the single-dose 28-day waiting period, the next cohort will be started at the next planned single dose level.

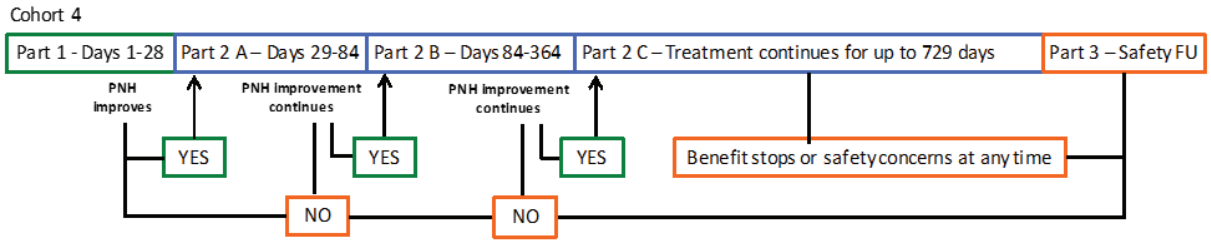
For Cohort 3, subjects will receive SC APL-2 daily for 28 days at the corresponding multiple dose for their cohort. After both subjects in the preceding cohort have completed the 28-day dosing period, the next cohort will be started at the next planned dose level.

Study Outline



■ = APL-2 administration. SD = Single Dose. SMC = Safety Monitoring Committee.
SMC will review all available cumulative safety and PK data starting at the end of single dose period of cohort 1 single dose period and at approximately every 4 weeks thereafter until the end of multiple dosing of cohort 4. Additional, less frequent SMC meetings will be scheduled for the remainder of the study.

For Cohort 4, the treatment period will consist of three parts as outlined in the diagram below. In Part 1, subjects will receive APL-2 for 28 days. At Visit 30 on Day 29, subjects concluded to benefit from the treatment (as determined by the Investigator and Sponsor after reviewing the available data) will automatically enter into Part 2A and continue treatment for an additional 56 days (Days 29 to 84). At Visit 86 on Day 85, subjects continuing to benefit from the treatment (as determined by the Investigator and Sponsor after reviewing the available data) will automatically enter into Part 2B and continue treatment for an additional 309 days (Days 85 to 364).



9.3.1 Safety Monitoring Committee

An external, independent Safety Monitoring Committee (SMC) will review cumulative safety/tolerability data (e.g., physical examinations, electrocardiograms [ECGs], vital signs, clinical laboratory tests, and adverse events [AEs]) and PK data including predicted exposures for subsequent doses based on emerging PK data and will have the responsibility to conduct a thorough safety assessment at regular (monthly) intervals during the dose escalation phase of the study. A key responsibility of this committee will be to make a recommendation whether to continue, modify or stop dose escalation (or the study) based upon an evaluation of emerging safety data, in particular Adverse Events of Special Interest as outlined in Section 11.5. The SMC

will comprise at least of a Hematologist with PNH experience and an Infectious Disease Specialist. The SMC will meet regularly as defined in the SMC charter, commencing before initiation of Cohort 2. Dose escalations and continuation beyond 28 days (Cohort 4) will not always coincide with SMC meetings. Additional regular or ad-hoc safety reviews will be scheduled as recommended by the committee or requested by the Sponsor.

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

9.4 Removal of Subjects from the Study

Subject participation in this trial may be discontinued for any of the following reasons:

1. Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol.
2. Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the PI that continued participation is not in the best interest of the subject.
3. Subject's decision to withdraw.
4. Subject failure to comply with protocol requirements or study related procedures.
5. Termination of the study by the Sponsor, FDA, or other regulatory authorities.

The clinical report will include reason(s) for subject withdrawals as well as details relevant to the subject withdrawal. If a subject is withdrawn from the trial prior to study completion, the subject will undergo all procedures scheduled for study completion (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 PI or a monitoring physician and will be treated and/or followed until the symptoms or values return to normal or acceptable levels, as judged by the PI.

Subjects withdrawn will not be replaced.

10. ASSESSMENTS

10.1 Safety Assessments

This study primarily assesses the safety and tolerability of APL-2. Safety will be determined by evaluating physical examinations, vital signs, ECGs, clinical laboratory parameters, injection site reactions and AEs as outlined in the Study Flow Chart in Section 2.

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

10.1.1 Body Height and Weight

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

10.1.2 Physical Examination

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

A licensed physician employed at the study site will examine each subject as outlined in the Study Flow Chart in Section 2.

Medical history will be recorded at screening.

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

10.1.3 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate will be measured as outlined in the Study Flow Chart in Section 2.

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.

On dosing days, vital signs will be measured pre- and post-dose. Vital signs will be measured within 2 hours prior to dosing for the pre-dose time point. Post-dose vital signs will be performed within approximately 30 minutes after dosing.

10.1.4 Electrocardiogram Monitoring

Single 12-lead ECGs will be measured at the time points outlined in the Study Flow Chart in Section 2.

On dosing days, 12-lead ECGs will be performed post-dose within approximately 30 minutes after completion of dosing.

ECG time points will be guided by PK data and will be collected around the estimated T_{max}. The time points may be changed depending on PK information obtained from previous cohorts. ECGs will be taken following resting in the supine position for 10 minutes in a quiet environment.

ECGs will be interpreted, signed and dated by the PI. 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, PQ or PR interval, QRS duration, and QT interval (corrected using both Bazett's and Fredericia's method and uncorrected) will be noted on the CRF. All CS findings will be recorded as AEs.

10.1.5 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 on Days 1 and 15 in Part 1; Days 29, 43, and 71 in Part 2A; Days 86,

142, 198, 253, and 309 in Part 2B; Days 533 and 729 in Part 2C and during the Exit Visit on Day 785 (see Appendix 1 for details).

10.1.6 Clinical Laboratory Tests

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

10.1.6.1 Hematology

- Hemoglobin
- Hematocrit
- Red blood cell (RBC) count
- Platelet count
- White blood cell (WBC) count with differential

10.1.6.2 Coagulation

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

10.1.6.3 Serum Chemistry

- BUN
- Creatinine
- Estimated creatinine clearance (using Cockcroft-Gault formula) – screening only
- Bilirubin (total and direct)
- Uric acid
- Albumin
- Alkaline phosphatase (ALP)
- Lactate dehydrogenase (LDH)
- Creatine kinase
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Gamma glutamyl transpeptidase (GGT)
- Glucose
- Sodium
- Potassium
- Chloride

10.1.6.4 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.

10.1.6.5 Serology

- HIV
- HCV
- HBsAg

10.1.6.6 Human Chorionic Gonadotropin (Serum Pregnancy Test) and Follicule-Stimulating Hormone

Serum Pregnancy Test will be performed for females only. FSH will be performed for postmenopausal females at screening only.

10.1.7 Injection Site Assessment

An assessment of the APL-2 injection site will be performed at each dosing day, within 30 min after completion of study drug administration. The assessment will be performed by a physician or other licensed health care provider (i.e. study nurse) as delegated by the PI. The injection site and the surrounding area will be inspected for redness, swelling, or induration; and the subject will be queried about the presence of pain and/or tenderness (See Appendix 2 for details). The date, time, and outcome of the injection site assessment will be recorded on the source documents and CRFs. Any abnormal findings will be reported as adverse events according to protocol Section 11.

10.2 Pharmacokinetic Assessments

10.2.1 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 Study Flow Chart in Section 2.

The allowable post-dose deviation window is as follows:

Sample time	Allowed deviation
Sampling ≤72 hours after first multiple dosing	±30 minutes
Sampling >72 hours	±10%

PK samples during multiple dosing will be collected pre-dose.

Preliminary PK analysis may be performed to reconsider sampling time points as the study progresses or to guide the dose escalation decision.

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

10.2.2 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.

10.3 Pharmacodynamic Assessments

Blood samples will be collected via direct venipuncture at the time points delineated in the Study Flow Chart in Section 2 for PD assessment of complement activation through the classical (e.g., CH50) and alternative (e.g., AH50) pathways, PNH clone distribution, C3 deposition on RBCs and Th17/Treg profile. Blood samples will also be collected to measure C3 levels. Other relevant PD markers may also be assessed.

Preliminary PD analysis may be performed to reconsider sampling time points as the study progresses or to guide the dose escalation decision.

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

10.4 Blood Volume for Study Assessments

Table 2: Blood Volume during Study (up to Visit 372)

Assay	Number of Time Points *	Approximate Volume per Time Point ** (mL)	Approximate Sample Volume Over Course of Study (mL)
Pharmacokinetics	32	2	64
Anti-APL-2 Ab assay	20	2	40
Hematology	29	3	87
Chemistry (Incl. screen serology and pregnancy)	29	6	174
Coagulation profile	26	4.5	117
Complement profile (C3, CH50 and AH50)***	28	4	112
Flow cytometry for PNH and C3 deposition	28	2	56
Th17/Treg Analysis	10	19	190
Free hemoglobin	28	2	56
		Total Blood Volume for Study	**896 mL**

* If the dose of APL-2 is increased above 270 mg/day, an additional 15 mL blood will be collected at up to three time-points, and the total blood volume for the study will increase to a maximum of 941 mL.

* Represents the largest collection volume planned over the duration of the study (smaller tubes will be used whenever possible).

** AH50 and AP50 both measure the hemolytic activity of alternative pathway of complement in blood samples. AH50 is reported in this study and AP50 has been used in other studies noted in this protocol.

10.5 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 at Visit 2 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. A final urine pregnancy test will be performed at the final Exit visit (Visit 372 or early termination). Male subjects will be counseled to avoid donating sperm after dosing at Visit 2 until the final Exit visit.

11. ADVERSE EVENTS

11.1 Definitions

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.

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 at Visit 2 will be categorized as pre-treatment events. Treatment-emergent adverse events (TEAEs) will be defined as those AEs that occur after dosing at Visit 2 and up to 30 days after the last dose of study medication.

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.

11.2 Recording Adverse Events

Subjects will be monitored for adverse events throughout the study. Adverse events may be volunteered spontaneously by the study subject, or discovered by the study staff during physical examinations, or by asking open, non-leading questions (e.g. “How have you been feeling since the last clinic visit?”). Subjects will be instructed to inform the investigator and/or study staff of any AEs that may occur at any time during the study.

All AEs occurring from screening through the final Exit visit will be recorded in detail in the source documents and documented on the appropriate AE or SAE eCRF. The nature of the AE, date (and time, if known) of AE onset, duration, severity, and action taken will be documented, together with the investigator’s assessment of the seriousness of the AE and relationship to study drug. All AEs should be recorded in the study subject’s own words (verbatim), unless in the opinion of the Investigator, the AE constitutes a recognized condition, disease, or syndrome. In that case, the condition, disease or syndrome should be named rather than the individual symptoms. The AEs will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA).

Outcome will be recorded as:

- Ongoing
- Resolved
- Resolved with sequela
- Death or
- Unknown

11.3 Assessment of Adverse Events

Each AE will be assessed by the Investigator or physician designee with regard to the categories discussed in the sections below.

11.3.1 Intensity

The Investigator will determine the severity of each AE. Localized injection site reactions will be closely monitored and will be graded according to the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Trials (FDA, 2007). See Appendix 2 for details.

- All other AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The following definitions for rating severity will be used:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)*.
Grade 3	Severe or 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.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE

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

*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.

When changes in intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted for that day. Any change in severity of signs and/or symptoms over a number of days will be captured and recorded as a new AE, with the amended severity grade, and the date and time (if known) of the change.

11.3.2 Causality

The relationship of an AE to the study drug will be assessed using the following criteria:

Unrelated	• Does not follow a reasonable temporal sequence from the administration of study drug • The event or laboratory test abnormality is clearly due to extraneous causes (disease, other drugs, environment, etc.)
Unlikely	• Does not follow a known pattern of response to study drug • Does not follow a reasonable temporal sequence from the administration of study drug • Disease or other drugs provides plausible explanation • It does not reappear or worsen when study drug is re-administered
Possibly	• Follows a known pattern of response to study drug • Time sequence from administration of the study drug is reasonable • Could also be explained by disease or other drugs
Probably	• Follows a known pattern of response to study drug • Time sequence from administration of the study drug is reasonable • Response to withdrawal clinically reasonable • Cannot be reasonably explained by the known characteristics of the participants clinical state, environmental factors, or other therapies administered to the subject

11.3.3 Serious Adverse Event

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening: this means that the subject was at risk of death at the time of the event; it does not mean that the event might have caused death had it occurred in a more severe form;
- Required hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Is a congenital anomaly or birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the 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.

Medical and scientific judgment should be exercised in deciding if an AE is serious and if expedited reporting is appropriate.

11.4 Reporting Serious Adverse Event

The reporting period for adverse events begins as soon as the subject's written consent to participate in the study has been obtained, and continues through the final Exit visit. The Investigator is responsible for reporting all SAEs to the Safety Monitor, whether or not the event is considered related to the study drug.

If an SAE occurs, the Investigator should complete and sign the SAE Report Form, and fax it to the Safety Monitor at the number listed below within 24 hours of becoming aware of the event:

Telephone No.: PPD

Telephone No.: PPD

Toll Free No.: PPD

Facsimile No.: PPD

The initial SAE Report should include, at a minimum, the following information:

- Study number
- Subject ID number
- Gender
- Date of birth
- Name of PI and full clinical site address
- Details of SAE
- Criterion for classification as "serious"
- Study drug name and treatment start date
- Date of SAE onset

- Causality assessment (if sufficient information is available to make this determination)

The Safety Monitor will request clarification of omitted or discrepant information from the initial report. The Investigator or designee is responsible for faxing the requested information to the Safety Monitor within 24 hours of the request.

Initial reports of SAEs must be followed later with detailed descriptions, including clear copies of supporting documents as necessary (e.g. hospital discharge summary, laboratory reports, autopsy reports, etc.), with the subject's personal identifiers removed. If a new SAE Report Form is faxed, the Investigator must sign and date the form.

The Investigator must report all SAEs to the IRB/IEC according to the institutional IRB/IEC policy.

11.5 Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical concern specific to the Sponsor's product or program where ongoing monitoring and rapid communication by the PI to the Sponsor may be appropriate. These adverse events may be serious or non-serious. Applicable adverse events may require further investigation in order to characterize and understand them, and depending upon the nature of the event, rapid communication by the Sponsor to other parties may also be required. These adverse events of special interest must be reported promptly to the sponsor. The adverse events of special interest include the following:

- Local or systemic infection of any origin
- Clinically significant decrease in kidney function
- Injection site reactions
- Thromboembolic events
- Infusion pump related events

If an AESI occurs in a study subject, the study subject will be followed for resolution of the adverse event. A decision will be made by the Sponsor concerning further exposure to the study treatment and further participation in the study.

11.6 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.

11.7 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 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. 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.

11.8 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.

Women of child-bearing potential (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 7.1.1) for the duration of the study.

If a female subject or partner of a male subject becomes pregnant during the study, the Investigator should report the pregnancy to the Safety Monitor within 24 hours of being notified. The subject or partner should be followed by the Investigator until completion of the pregnancy. At the completion of the pregnancy, the Investigator 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 Investigator should follow the procedures for reporting an SAE (Section 11.4).

12. STATISTICS

12.1 Sample Size Justification

The sample size was chosen to be sufficient to address safety, tolerability and PK analyses. All collected data will be enumerated in listings, summary data will be tabulated, and no formal statistical testing is planned for the study data.

12.2 Statistical Analysis Methodology

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

12.2.1 Study Analysis Datasets

The intent-to-treat (ITT) analysis set will be the primary analysis set for the efficacy endpoint; safety analysis set will be used for all safety assessments.

12.2.1.1 Intent To Treat (ITT)

The ITT population will include all subjects enrolled and eligible to receive study medication. The ITT population will be analyzed only for the purpose of subject disposition.

12.2.1.2 Safety

The safety population will include all ITT subjects who receive at least one dose of the study drug. The safety population is also referenced as the modified ITT (mITT) population. The mITT population is the primary population for efficacy and safety evaluations.

12.2.1.3 PK population

The PK population will include all safety population subjects who have had at least one PK sample drawn.

12.2.1.4 Data Review for Analysis Datasets

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 populations. The review will also check the quality of the data, identifying outliers, and making decisions on how to deal with problems in any data (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.

12.3 Study Endpoints

12.3.1 Efficacy Endpoint

The Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale (Version 4) is an exploratory efficacy endpoint for exploratory purposes only and no formal analysis of efficacy endpoint is planned for this study (see Appendix 1).

12.3.2 Safety Endpoints

The primary safety endpoints of the study are the number and severity of Treatment Emergent Adverse Events (TEAEs).

12.3.3 Pharmacokinetic Endpoints

The study endpoints are the plasma concentrations of APL-2 and pharmacokinetics parameters of APL-2 following administration of the single SC dose in relevant cohorts (Section 12.9).

12.4 Efficacy Analysis

The FACIT Fatigue Scale is a 13-item Likert scaled instrument. The FACIT instrument results in a score with a range of 0 to 52. The measure is collected at Visits described in the Study Flow Chart. The analysis of baseline score and change from baseline by cohort and time point will be

evaluated. No imputation for any missing data will be planned. An exploratory efficacy analysis of the FACIT data and relevant PD markers will be presented.

12.5 Safety Analysis

All safety endpoints will be evaluated using the safety population. No formal inferential statistics will be applied to the safety assessments.

12.5.1 Total Exposure

By-patient study drug exposure (date/time of injection, injection site, injection volume) will be presented in a listing.

12.5.2 Adverse Events

Treatment emergent adverse events (TEAE) 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 Medical Dictionary for Regulatory Activities (MedDRA) will be used to classify all AEs.

12.5.2.1 Adverse Events Summary

A by-subject TEAE data listing, including verbatim term, preferred term, treatment, severity, and relationship to treatment will be provided. Serious adverse events (SAEs), adverse events of special interest (as defined in Section 11.5), and details of subjects withdrawing due to adverse events will also be listed.

AEs will be tabulated as a total population and by treatment group. For Cohort 1 and Cohort 2, reported tables will also consider the dosing phase for the AE. The following will be tabulated:

1. Topline summary of Adverse Events, tabulating the number of TEAEs, treatment related AEs, Serious AEs, AEs of special interest, injection site reactions, and adverse events leading to discontinuation
2. TEAEs by SOC and preferred term
3. TEAEs regarded as possibly/probably related to study drug by SOC and preferred term
4. TEAEs and Serious AEs by maximum severity, and by SOC and preferred term
5. Adverse events of special interest by maximum severity and relationship to study drug

12.5.3 Clinical Laboratory Tests

All laboratory endpoints will be summarized in listings. In addition, laboratory values that are above or below the reference range will be identified in the listings.

12.5.4 Vital Signs

Vital signs will be listed for each subject and time point. Any Investigator determined potential clinically significant findings will be identified and listed.

12.5.5 ECGs

ECG results will be classified using frequency counts for normal, abnormality that is not clinically significant (NCS), and clinically significant abnormality (CS) by cohort and time point of collection. ECGs results will be listed for each subject and each time point. Any Investigator determined potential clinically significant changes will be identified and listed.

12.6 Handling of Dropouts and/or Missing Data

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

12.7 Examination of Subgroups

Due to the potentially small sample size in any subgroup analyses performed will use descriptive statistics only; no tests of hypotheses will be performed.

12.8 Enumerated Data

Physical Examination and changes in physical examinations findings after baseline will be reported in a listing.

Concomitant medications will be listed by treatment and coded using the most current WHO drug dictionary.

Medical history findings will be coded using latest MedDRA dictionary and listed by subject.

12.9 Pharmacokinetic Analysis

All subjects dosed and having any measurable serum concentration of study drug will be included in the PK data set.

The individual plasma concentration profiles of APL-2 after single dose phase (for Cohorts 1 and 2) and multiple dose phase (for all cohorts) will be listed and plotted.

Where possible, in Cohort 1 and Cohort 2, PK parameters for APL-2 will be computed from the individual serum concentrations-time data during the single dose phase, using actual sample times. PK parameters will be listed, but not summarized.

AUC_{0-t}	The area under the serum concentration versus time curve, from time 0 to the last measurable concentration prior to the start of multiple dosing, as calculated by the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing.
C_{max}	Maximum observed serum concentration.
t_{max}	Time of the maximum measured serum concentration. If the maximum value occurs at more than one time point, t_{max} is defined as the first time point with this value.

Additional PK analyses may be performed. Any analyses or presentations will be outlined in the Statistical Analysis Plan.

12.10 Pharmacodynamic Analysis

All subjects dosed and having any measurable PD data will be included in the PD data set.

PD parameters include Lactate Dehydrogenase (LDH), Haptoglobin, Hemoglobin, serum levels of CH50, AH50, and C3, and clonal distribution of PNH cells. These data will be listed by subject and cohort along with changes from baseline and percent changes from baseline. Individual changes and percent changes from baseline will be plotted against assessment.

Red blood cell transfusion data will also be listed by subject and cohort.

12.11 Antigenicity Analysis

APL-2 antigenicity will be assayed in a GLP-compliant manner using a validated direct ELISA-based method incorporating a mouse monoclonal antibody specific for PEG as a positive control that is capable of detecting extremely low amounts of anti-PEG and APL-2 antibodies, typically in the sub-µg/ml concentration range. This anti-PEG monoclonal antibody will be included as positive controls on every ELISA test plate run in these studies.

12.12 Interim Analysis

As mentioned in Section 9.3, a safety review committee will be formed to review safety/tolerability, PK and PD data between cohorts. Preliminary PK analysis may also be performed to reconsider sampling time points as the study progresses.

When all subjects have completed (or discontinued) Part 2A or Part 3 if they didn't enter Part 2A, the data collected up to and including these study visits will be reported. Further reports may be prepared with each report containing cumulative information. These reports will be performed on data that will have been fully checked and considered as final. Any changes to the data previously reported will be fully auditable and discussed in the subsequent reports.

12.12.1 Safety (optional)

At the Sponsor's request, safety tables, figures, and data listings may be presented to the sponsor's consultants for the purposes of planning the next Phase 1 or initial Phase 2 studies prior to database lock. These interim analyses will be performed on data that will be edit-checked and monitored.

A safety programmer and a biostatistician will prepare safety tables, figures, and data listings.

13. ADMINISTRATIVE CONSIDERATIONS

13.1 Direct Access to Source Data/Documents

The Investigator 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 Investigator will permit trial-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 Investigator 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.

13.2 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 Investigator, 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) 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.

13.2.1 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 Investigator will provide direct access to source data/documents for study-related monitoring. It is important that the Investigator 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 Investigator.

13.3 Ethics

13.3.1 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, GCP, 21 CFR Parts 50, 56, and 312, the ethical princliples set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

13.3.2 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 principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56) and/or ICH Guidelines, or other local regulations as deemed appropriate.

13.3.3 Subject Information and Consent

The Investigator is responsible for obtaining an informed consent. A written informed consent, in compliance with the US Code of Federal Regulations (21 CFR Part 50), 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 Investigator 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.

13.3.4 Confidentiality

Confidentiality of subjects information must be maintained in accordance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule-Final Modification (45 CFR Parts 160 and 164).

13.3.5 ClinicalTrials.gov

This study will be listed with ClinicalTrials.gov, as required.

13.3.6 Termination of Study

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

13.4 Data Handling and Record Keeping

The Investigator 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 Investigator/Institution as to when these documents no longer need to be retained.

13.5 Protocol Amendments

Any amendments to the study protocol deemed necessary as the study progresses will be discussed between Sponsor and the Investigator. The Investigator will not implement any changes to the protocol without an agreement by the Sponsor and prior review and documented approval/favorable opinion 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 Investigator and must be confirmed in writing. Amendment(s) will be approved and signed off in the same way as the protocol.

13.6 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).

13.7 Finance and Insurance

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

13.8 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 Investigator and Site personnel by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

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

14. REFERENCES

Note: A copy of the publications by DeZern (2013), Ivens (2013) and Rudmann (2013) referred to in this document is included in Item 10 and on the CD attached to the original IND submission.

1. Schrezenmeier et al. Baseline characteristics and disease burden in patients in the International Paroxysmal Nocturnal Hemoglobinuria Registry. Haematologica, 2014, 99 (5), p. 922-929.
2. Hillmen P, et al. Long-term effect of the complement inhibitor eculizumab on kidney function in patients with paroxysmal nocturnal hemoglobinuria. Am. J. Hematol., 2010, 85, p.553–559.
3. DeZern AE, Dorr D, and Brodsky, RA. Predictors of Hemoglobin Response to Eculizumab Therapy in Paroxysmal Nocturnal Hemoglobinuria, *Eur J Haematol.*, 2013, 90(1), p.16-24
4. Apellis Pharmaceuticals, Inc. APL-2. Investigator's Brochure. Version 5 April 2016.
5. FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. July 2005. Available online: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078932.pdf
6. FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. September 2007. Available online: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf
7. FDA Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies-Small Entity Compliance Guide. December 2012. Available online: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332846.pdf
8. Ivens, I. A., Baumann, A., McDonald, T. A., Humphries, T. J., Michaels, L. A., and Mathew, P. (2013). PEGylated therapeutic proteins for haemophilia treatment: a review for haemophilia caregivers. Haemophilia 19: 11-20
9. Rudmann, D.G., Alston, J.T., Hanson, J.C., and Heidel, S. (2013). High molecular weight polyethylene glycol cellular distribution and PEG-associated cytoplasmic vacuolation is molecular weight dependent and does not require conjugation to proteins. Toxicol Pathol 41: 970-983.
10. 2016 Adult Immunization Schedule was approved by the Centers for Disease Control and Prevention's (CDC). Fedruary 2016. Accessed on August 1st 2016. http://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf

15. APPENDIX 1: FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY (FACIT) FATIGUE SCALE

FACIT Fatigue Scale (Version 4)

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

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

FACIT-Fatigue Subscale Scoring Guidelines (Version 4)

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

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

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

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

Subscale	Item Code	Reverse item?		Item response	Item Score
FATIGUE	HI7	4	-	_____	=_____
SUBSCALE	HI12	4	-	_____	=_____
	An1	4	-	_____	=_____
	An2	4	-	_____	=_____
Score range: 0-52	An3	4	-	_____	=_____
	An4	4	-	_____	=_____
	An5	0	+	_____	=_____
	An7	0	+	_____	=_____
	An8	4	-	_____	=_____
	An12	4	-	_____	=_____
	An14	4	-	_____	=_____
	An15	4	-	_____	=_____
	An16	4	-	_____	=_____

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

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

16. APPENDIX 2: ASSESSMENT OF LOCAL INJECTION SITE REACTIONS

Local injection site reactions will be rated according to the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (Sep 2007)[3] as follows:

Local Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest
Erythema/Redness*	2.5 – 5 cm	5.1 – 10 cm	> 10 cm
Induration/Swelling**	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.