Inclusion Criteria

At Screening (unless otherwise specified)

- At least 18 years old (inclusive)
- Diagnosed with PNH (white blood cell (WBC) clone >10%)
- Lactose dehydrogenase (LD) ≥2 times the upper limit of normal
- Screening Ferritin ≥ normal and Total Iron Binding Capacity (TIBC) ≤ LLN based on central lab reference ranges. If a subject is receiving iron supplements at screening, the investigator must ensure that his/her dose has been stable for 8 weeks prior to enrolment and must be maintained throughout the study (see Section 8.4.4)
- Last transfusion within 12 months prior to screening
- Platelet count of >30,000/mm^3 at the screening visit
- Absolute neutrophil count >500/ mm^3 at the screening visit
- 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
- Vaccination against Neisseria meningitides types A, C, W, Y and B, Streptococcus pneumoniae and Haemophilus influenzae Type B (Hib) either within 2 years prior to Day 1 dosing, or within 14 days after starting treatment with APL-2. Unless documented evidence exists that subjects are non-responders to vaccination as evidenced by titers or display titer levels within acceptable local limits
- Willing and able to give informed consent

Exclusion Criteria

- Prior eculizumab (Soliris®) treatment
- Active bacterial infection
- Hereditary complement deficiency
- History of bone marrow transplantation
- Concurrent severe aplastic anemia (SAA), defined as currently receiving immunosuppressive therapy for SAA including but not limited to cyclosporin A, tacrolimus, mycophenolate mofetil or anti-thymocyte globulin
- Participation in any other investigational drug trial or exposure to another investigational agent, device or procedure within 30 days

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	37 to 42	43	44 to 56	57	58 to 70	71	72 to 84
Informed Consent										
Demographics										
Medical, transfusion, and thrombosis history										
Vaccination. A										
Review entry criteria										
Preventive antibiotic. B	X	X	X	X	X	X	X	X	X	X
Physical examination. C	X						X			
12-lead electrocardiogram. D	X		X		X		X		X	
APL-2 administration. E	**S**	**H**	**S**	**H**	**S**	**H**	**S**	**H**	**S**	**H**
Injection site assessment. F	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Vital sign measurements. G	X	X	X	X	X	X	X	X	X	X
Urinalysis	X		X		X		X		X	
Blood. I	X		X		X		X		X	
Pharmacokinetics. **I**	X				X				X	
Anti-APL-2 Ab assay	X								X	
Hematology and chemistry.	X		X		X		X		X	
Coagulation profile	X		X		X		X		X	
Complement profile (C3, CH50 and AP50)	X		X		X		X		X	
Flow cytometry for PNH/C3 deposition	X		X		X		X		X	
Plasma Hb	X		X		X		X		X	
Urine pregnancy test. J	X		X		X		X		X	
FACIT fatigue Scale	X				X				X	
LASA QoL	X				X				X	
Adverse events	X	X	X	X	X	X	X	X	X	X
Thrombosis record (MAVE). K	X	X	X	X	X	X	X	X	X	X

See footnotes below continuation flow chart

LLN	Lower Limit of Normal
MAC	Membrane attack complex
MAVE	Major Adverse Vascular Event
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mL	Millilitre(s)
MOP	Manual of Procedures
NCS	Not clinically significant
NOEL	No observed effect level
NOAEL	No observed adverse effect level
NZW	New Zealand White
PCV13	Pneumococcal conjugate vaccine
PD	Pharmacodynamic(s)
PEG	Polyethylene glycol
PEG40	Polyethylene glycol (40 kDa nominal molecular weight)
PI	Principal Investigator or designee
PK	Pharmacokinetic(s)
PPSV23	Pneumococcal polysaccharide vaccine 23
PT	Prothrombin time
PNH	Paroxysmal nocturnal hemoglobinuria
QTc	Corrected QT interval
QTcB	Bazett's correction
QTcF	Fridericia's correction
RBC	Red blood cell
SAA	Severe aplastic anaemia
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SMC	Safety Monitoring Committee
SOP	Standard operating procedure
$t_{½}$	Serum half-life
TEAE	Treatment-emergent adverse event
TK	Toxicokinetic(s)
ULN	Upper Limit of Normal
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 part of a series of studies for the clinical development of APL-2. The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and

- Part 2A: Following review of available safety, PK and PD data by the investigator and sponsor, subjects showing evidence of clinical benefit may progress to Part 2A of the study and continue to receive daily doses of APL 2 until Day 84.
- Part 2B: Following review of available safety, PK and PD data by the investigator and sponsor subjects showing evidence of clinical benefit may progress to Part 2B of the study and continue to receive daily doses of APL 2 until Day 364.
- Part 3: Safety follow up

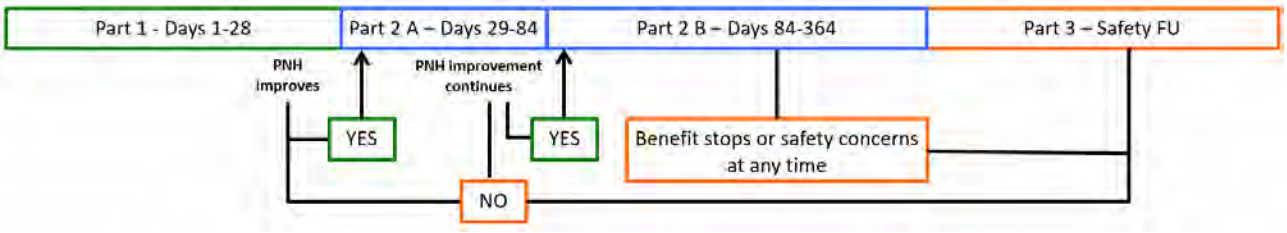
Screening will take place within 30 days prior to the start of dosing on Day 1.

Subjects will be entered into Part 1 of the study on Day 1 at a time designated by the PI. Research nurses or other appropriately qualified research personnel will administer the SC infusions for a minimum of 3 days (Days 1-3) until the research nurse considers that the subject is both capable and confident to conduct self- administration. The subject will continue to self-administer infusions at the clinic on those days when a clinic visit occurs (Day 8, 15 and 22) and at an off-site location convenient to the subject on all other days up to Day 28 in Part 1. 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 Day 84, and then may progress to Part 2B of the study and continue to receive daily doses of APL-2 until Day 364. Doses will be self-administered throughout this period at an off-site location convenient to the subject with the exception of Days 29, 36, 43, 57, 71, 85, 113, 141, 169, 197, 225, 253, 281, 309, and 337 where dosing is performed by the subject 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 during part 2A, and doses will be administered at the clinical site every 2 weeks for the first 6 weeks after commencing the higher dose. After the conclusion of the treatment period (Day 364), subjects will enter Part 3 of the study and return to the clinical site for follow-up study procedures on Day 365, 379, and 393 and final study procedures at an Exit Visit on Day 414. See Study Flowchart in Section 2.

The planned length of participation in the study for each subject is approximately 444 days (from Day –30 through completion of the Day 414 Exit visit procedures). Interim PK and PD analyses may be performed to reconsider the sampling time points as the study progresses.

An independent Safety Monitoring Committee (SMC) will assess the progress and cumulative safety/tolerability data of the study on a regular basis.

Continuation of treatment – Decision scheme



7. SUBJECT SELECTION

The study will be conducted alongside the ongoing Phase Ib study APL2-CP-PNH-204 (PADDOCK) to investigate APL-2 in PNH patients who have not previously received treatment with eculizumab. Safety and efficacy data from both studies will be used to support the data obtained in the Phase III confirmatory study. Up to 20 subjects will be enrolled to complete 28 days of dosing.

Cohort	Planned dosing schedule
Single cohort	270 mg/day (up to 360 mg/day from Day 29) from Day 1 to Day 364*

* The dose may be increased up to 360 mg/day during Part 2A if the clinical response is sub-optimal. The volume to be administered will depend on the final concentration provided and will be administered as a SC infusion.

The dose for this study was determined based on safety, PK, and PD data from the ongoing studies in PNH patients.

Intra-subject dose escalations will be agreed by the Investigator and Sponsor and will be implemented on an individual subject basis and not necessarily applied across all subjects in the cohort. The dose for an individual subject will not exceed 360 mg/day (estimated to reach approximately 85 % of the C_{max} of the NOAEL observed in monkeys) without a protocol amendment.

8.3.3 Drug Administration

All doses will be administered as SC infusions.

The preferred site of injection will be the abdomen; however, if a subject does not tolerate administration into the abdomen alternative sites may be selected e.g. thigh or upper arm. Subjects will self-administer the SC infusions after receiving appropriate training by a research nurse or other study 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.

Doses will be administered while subjects are seated.

Dosing records will be maintained at the clinical site and available for review by the sponsor.

8.4 Concomitant Medications

8.4.1 Prophylactic antibiotics

Prophylactic antibiotic therapy will be prescribed to all subjects to minimize potential infection risk. Prophylactic antibiotics will be initiated on day 1 following administration of APL-2 dosing and continue until 2 weeks after the last dose.

8.4.1.1 Primary prophylactic antibiotic Day 1-14

- Ciprofloxacin 500 mg twice daily, initial administration on Day 1 will take place at the initial APL-2 dosing, following ECG collection postdose.

8.4.1.2 Primary prophylactic antibiotic Day 15 onwards

- 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 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.

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 up until the symptoms or values return to normal or acceptable levels, as judged by the PI.

Subjects who are withdrawn may be replaced. Replacement of subjects will be discussed on a case by case basis.

10. ASSESSMENTS

10.1 Assessments

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

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

10.1.1 Body Height and Weight

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

10.1.2 Physical Examination

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

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.

At clinic visits 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 readings will be performed within approximately 30 minutes after dosing.

10.1.4 Electrocardiogram Monitoring

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

If done on dosing days, ECGs will be performed within approximately 30 min after dosing.

ECGs will be taken following resting in the supine position for 10 min in a quiet environment.

ECGs will be interpreted and 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 Fridericia'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 as outlined in the Study Flow Chart in Section 2. The subject is presented with 13 statements and is asked to indicate their response as it applies to the past 7 days. The 5 possible responses are 'Not at all' (0), 'A little bit (1), 'Somewhat' (2), 'Quite a bit' (3) and 'Very much' (4). With 13 statements the total score has a range of 0 to 52. Before calculating the total score, some responses are reversed to ensure that the higher score corresponds to a higher quality of life. The FACIT Fatigue Scale and scoring guidelines are provided in the Manual of Procedures (MOP).

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

The Linear Analog Scale Assessment (LASA) consists of three items asking respondents to rate their perceived level of functioning. Specific domains include activity level, ability to carry out daily activities, and an item for overall QOL. A representation of the scale is presented in Appendix 2 (see Appendix 2). LASA is self-administered by the subjects during clinic visits as outlined in the Schedule of Events in Section 2. Scores for the three individual components of the scale and the combined score will be included in the analysis and this will be described in the Statistical Analysis Plan.

10.1.7 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 or recommended by the SMC. The clinical laboratory tests include (but are not limited) the following:

10.1.7.1 Hematology

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

10.1.7.2 Coagulation

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

10.1.7.3 Serum Chemistry

- Blood urea nitrogen (BUN)
- Creatinine
- Estimated creatinine clearance (using Cockcroft-Gault formula) – screening only
- Bilirubin (total and direct)
- Albumin
- Aspartate aminotransferase (AST)
- ALT
- Uric acid
- Glucose
- Sodium

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 Flow Cytometry Assessments

Blood samples will be collected via direct venipuncture at the time points delineated in the Study Flow Chart in Section 2. Flow cytometry assessment will include, but not be limited to: PNH clonal distribution of RBCs, CD71+ immature reticulocytes, monocytes and granulocytes and C3 deposition on RBCs.

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

10.4 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., AP50) pathways. Blood samples will also be collected to measure C3 levels. Other relevant PD markers may also be assessed.

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

10.5 Anti- APL-2 Antibody Assessment

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

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

10.6 Blood Volume for Study Assessments

Table 2: Blood Volume during Study (up to Day 414)

Assay	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Pharmacokinetics	19	2	38
Anti-APL-2 Ab assay	9	2	18
Hematology	20	3	60
Chemistry (Incl. screen serology and pregnancy)	20	3	60
Coagulation profile	20	4.5	90
Complement profile (C3, CH50 and AP50)	20	4	80
Flow cytometry for PNH and C3 deposition	20	2	40
Plasma Hb	20	4	80
Total Approximate Blood Volume for Study:			**466****

- *** Represents the largest collection volume planned over the duration of the study (smaller tubes will be used whenever possible).**
- **** If dose is increased to 360 mg/day, additional blood draws will be scheduled.**

10.7 Pregnancy tests

For WOCBP, a serum pregnancy test will be performed at screening, and subjects with a positive test will be excluded from the study. A follow up urine pregnancy test will be performed on Day 1 pre-dose (a negative urine pregnancy test must be received before dosing with study drug). A urine pregnancy test will also be performed at each site visit (pre-dose) if applicable. A final urine pregnancy test will be performed at the final Exit Visit. Male subjects will be counseled to avoid donating sperm after dosing on Day 1 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 on Day 1 will be categorized as pre-treatment events. Treatment-emergent adverse events (TEAEs) will be defined as those AEs that occur after dosing on Day 1 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 PI’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 PI, 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 PI or physician designee with regard to the categories discussed in the sections below.

11.3.1 Intensity

The PI will determine the severity of each AE. 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:

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

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, or 30 days after the final dose of study medication. The PI 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 PI should complete and sign the SAE Report Form, and fax or email it to the Safety Monitor at the number/address which will be provided separately to the investigator sites, within 24 hours of becoming aware of the event:

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

- Study number
- Subject number/ID
- 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, or designee, will request clarification of omitted or discrepant information from the initial report. The PI or designee is responsible for emailing or 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 PI must sign and date the form.

The PI 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 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, and depending upon the nature of the event, rapid communication by the trial 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
- Thrombosis
- Clinically significant decrease in kidney function
- Injection site reactions

If an adverse event of special interest 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 up until the symptoms or value(s) return to baseline or are clinically stable. Treatment of AEs will be performed by appropriately trained medical personnel, either at the clinical site or at a nearby hospital emergency room. When appropriate, medical tests and/or examinations will be performed to document resolution of the event(s).

AEs continuing after completion of the study will be followed up by telephone or with visits per the discretion of the PI. 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. Pregnancies will be reported using a pregnancy report form.

WOCBP and males with female partners of child-bearing potential will be instructed to practice an acceptable method of birth control (as defined in Section 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 PI should report the pregnancy to the Safety Monitor within 24 hours of being notified. The subject or partner should be followed by the PI until completion of the pregnancy. At the completion of the pregnancy, the PI will document and report the outcome. If the outcome of the pregnancy meets the criteria for classification as an SAE (i.e. postpartum complication, stillbirth, neonatal death, or congenital anomaly) the PI should follow the procedures for reporting an SAE (Section 11.4).

12. STATISTICS

12.1 Sample Size Justification

The study will be conducted alongside the ongoing Phase Ib study APL2-CP-PNH-204 (PADDOCK) to investigate APL-2 in PNH patients who have not previously received treatment with eculizumab. Safety and efficacy data from both studies will be used to support the data obtained in the Phase III confirmatory study. Up to 20 subjects will be enrolled to complete 28 days of dosing. The sample size is considered sufficient to obtain useful safety, tolerability, PD and PK data to support the clinical program.

12.2 Statistical Analysis Methodology

A formal Statistical Analysis Plan (SAP) will be developed and finalized prior to locking the database. The full details of data presentations and analyses will be provided therein. Additional statistical analyses other than those described in this section may be performed if deemed

appropriate and included in the SAP. Any deviations from the final analysis plan or from what is outlined in the protocol will be discussed in the final study report.

No formal inferential statistics will be applied to data collected in the study.

The data from this study will also be pooled with the Cohort 2 data from the Phase Ib study APL2-CP-PNH-204 (PADDOCK), which also investigates 270mg/day APL-2 in PNH patients who have not previously received treatment with eculizumab. The details of reporting this pooled data will be documented in a separate SAP.

12.2.1 Analysis Populations

12.2.1.1 Screened Population

The Screened Population will include all subjects who signed the informed consent form and are screened for participation in this study. This set will be used only for the purpose of describing subject disposition.

12.2.1.2 Safety Population/ Intent to Treat (ITT) Population

The Safety Population will include all subjects eligible to receive study medication and who receive at least one dose of study medication. The Intent to Treat Population will be identical to the Safety Population for this study. All baseline characteristics, demographic and efficacy endpoint data will be presented using the ITT Population.

12.2.1.3 Pharmacokinetic (PK) Population

The PK Population will include all subjects in the Safety Population who have at least one quantifiable concentration of APL-2.

12.2.1.4 Pharmacodynamic (PD) Population

The PD Population will include all subjects in the Safety Population who have at least one quantifiable post dose PD parameter.

12.2.1.5 Data Review for Analysis Populations

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.

12.2.2 Study Endpoints

12.2.2.1 Safety Endpoints

The primary safety endpoints of the study are the number and severity of TEAEs. Safety will also be assessed through vital signs, 12-lead ECG and laboratory safety data. Changes from baseline will be calculated using the last measurement prior to the start of dosing as baseline.

12.2.2.2 Efficacy Endpoints

Changes from baseline and percentage changes from baseline in LD, haptoglobin and Hb are the primary efficacy endpoints. They will be calculated for each post dose assessment, where the baseline will be taken as the last measurement prior to the start of dosing.

12.2.2.3 Secondary Endpoints

Secondary endpoints include:

- changes from baseline in FACIT Fatigue Scale (Version 4)
- changes from baseline and percentage changes from baseline in reticulocyte count
- changes from baseline and percentage changes from baseline in total bilirubin
- changes from baseline in the number of RBC transfusions per month and number of units transfused per month
- changes from baseline in LASA scale scores (individual and combined).

Baseline will be taken as the last measurement prior to the start of dosing. For transfusions baseline will be taken from the 12 month transfusion history.

12.2.2.4 Pharmacokinetic Endpoints

Plasma concentrations of APL-2 will be determined from multiple samples taken between Day 1 and the Exit Visit.

12.2.2.5 Exploratory Pharmacodynamic Endpoints (Markers)

Changes from baseline and percentage changes from baseline will be calculated for each of the complement parameters (CH50, AP50 and C3), C3 deposition on RBC cells and clonal distribution of PNH RBCs. Baseline will be taken as the last measurement prior to the start of dosing.

12.2.3 Safety Analyses

All safety endpoints will be evaluated using the Safety Population.

12.2.3.1 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.

TEAE will be summarized by system organ class and preferred term. Tabulations will be produced for all TEAEs, for those considered potentially treatment related (causality to study drug is reported as possibly or probably, or where causality is not reported) and for TEAE of special interest. Number of subjects reporting SAEs will also be tabulated.

A by-subject TEAE data listing, including verbatim term, preferred term, treatment, severity, and investigator judgment of relationship to treatment, will be provided.

12.2.3.2 Clinical Laboratory Tests

A by-subject listing will be provided including changes from baseline. Laboratory values that are outside the laboratory reference range will be flagged.

12.2.3.3 Vital Signs and ECGs

Observed and change from baseline values for vital sign and ECG parameter will be listed.

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

12.2.4 Efficacy and Secondary Endpoint Analyses

The efficacy and secondary endpoints will be evaluated for the ITT Population.

Absolute values, changes from baseline and percentage changes from baseline (where appropriate) will be summarised, using descriptive statistics, by study visit. Data will be plotted by study day.

The number of RBC transfusions per month and number of units transfused per month will be summarized over the study.

12.2.5 Pharmacokinetic Analyses

The PK concentrations will be evaluated using the PK Population.

Individual concentration over time profile plots will be presented. Median profiles of the concentration-time data, using nominal sampling times, will also be presented. Both linear-linear and linear-log plots will be presented. APL-2 concentrations will be summarized by study visit using descriptive statistics.

Where appropriate, steady-state PK parameters for APL-2 will be estimated from the individual serum concentrations-time data, using actual sample times using a non-compartmental approach. PK parameters will include:

AUCtotal: The area under the serum concentration versus time curve, from time 0 (pre-dose Day 1) to the last measurable concentration (t) at the end of study.

Ctrough,max: Maximum observed pre-dose serum concentration.

PK parameters will be summarized using descriptive statistics.

PK data will be combined with the prior data collected in earlier clinical studies and then used to update the APL-2 population PK model (Apellis Data on File).

12.2.6 Pharmacodynamic Analyses

The PD parameters will be evaluated using the PD Population.

Absolute values, changes from baseline and percentage changes from baseline will be summarised, using descriptive statistics, by study visit. Individual parameter over time profile plots will be presented. Median profiles over time, using nominal sampling times, will also be presented.

12.2.7 Handling of Dropouts and/or Missing Data

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

Where appropriate screen values may be used as baseline in the event of missing Day 1 measurements.

Missing dates/times will be reviewed on a case by case basis for potential imputations, but the original data will always be presented in data listings.

PK concentration values below the limit of quantification will take the value of 0 in individual linear-linear profile plots and the limit of quantification in linear-log profile plots.

12.2.8 Other Data Analyses

Demographic data, baseline characteristics, physical examination, concomitant medication and medical history data will be listed. The current versions of the World Health Organization (WHO) and MedDRA coding dictionaries will be used for the concomitant medications and medical histories respectively.

12.3 Interim Analyses

As mentioned in Section 9.6, a periodic safety review will take place on a regular basis by the SMC to review safety/tolerability, PK and PD data.

Data may be reported while the study is ongoing to help guide decisions to further develop APL-2. 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 subsequent reports.

13. ADMINISTRATIVE CONSIDERATIONS

13.1 Direct Access to Source Data/Documents

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

The PI will permit 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 PI will ensure that the auditor is allowed direct access to the source data, medical records, eCRFs, and the Site's regulatory file for the study and any other pertinent information.

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 PI, Sponsor and/or its' designee are responsible for ensuring that the study staff receive appropriate training on the protocol, study procedures and any other relevant information.

Quality assurance and quality control systems are implemented and maintained using written Investigative site, Sponsor and/or designee Standard Operating Procedures (SOPs) to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s) 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 PI will provide direct access to source data/documents for study-related monitoring. It is important that the PI and the staff are available at these visits. The monitor will record the date of each visit together with a summary of the status and progress of the study. Proposed actions will be documented in writing to the PI.

13.3 Ethics

13.3.1 Ethical Conduct of the Study

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

- Evidence of QTcF prolongation defined as >450 ms for males and >470 ms for females at screeningBreast-feeding women
- History of meningococcal disease

Endpoints

Primary Safety Endpoint:

The primary safety endpoints of the study are the number and severity of treatment emergent adverse events (TEAEs) following administration of multiple doses of SC APL-2.

Primary Efficacy Endpoints:

- Change from baseline in LD
- Change from baseline in Haptoglobin
- Change from baseline in Hemoglobin (Hb)

Secondary Endpoints:

- APL-2 plasma concentrations (and pharmacokinetic (PK) parameters as appropriate)
- Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale score
- Change from baseline in reticulocyte count
- Change from baseline in total bilirubin
- Change from baseline in Linear Analog Scale Assessment (LASA) for Quality of Life
- Number of red blood cell (RBC) transfusions per month

Exploratory PD markers include:

- Complement (CH50, AP50, and C3) levels
- C3 deposition on RBC cells
- Clonal distribution of PNH RBCs

Planned Dose Levels

The planned dose for this single cohort study will be a daily dose of 270 mg/day however from Part 2A onwards intra-subject dose escalation up to a dose of 360 mg/day may be permitted.

The dose was determined based on cumulative safety, PK, and PD data from ongoing studies in PNH patients.

Safety data from this study will be reviewed by the SMC on a regular basis.

Study Design

This is a Phase IIa, open-label, multiple dose, study in patients with PNH who have not received eculizumab (Soliris®) in the past. A single cohort is planned for evaluation.

Study Period	**Part 2B - Treatment (Daily from Day 85 to Day 364) (L)**											
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
Vaccination	X											
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			
Hematology and chemistry.	X		X		X		X		X		X	
Coagulation profile	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	
Plasma Hb	X		X		X		X		X		X	
Urine pregnancy test. J	X		X		X		X		X		X	
FACIT fatigue Scale	X				X				X			
LASA QoL Scale	X				X				X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Thrombosis record (MAVE) K	X	X	X	X	X	X	X	X	X	X	X	X

See footnotes below continuation flow chart

applicable regulatory requirements. The subject population will be comprised of adult male and female subjects with paroxysmal nocturnal hemoglobinuria (PNH).

4.1.1 Paroxysmal Nocturnal Hemoglobinuria

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

Any therapy that effectively inhibits MAC formation is anticipated to be a plausible candidate-treatment for PNH. Indeed, eculizumab is a monoclonal anti-C5 antibody that inhibits the formation of the MAC, and eculizumab treatment has been approved for the treatment of this serious condition. However, inhibition of MAC formation does not appear to be sufficient to fully control the disease, as many PNH patients receiving eculizumab treatment still suffer from anemia, with only roughly 13% of patients being classified as complete responders, i.e. achieving transfusion independence and normal Hb levels. Most of the patients (53%) were classified as partial responders with decreased transfusion needs and reduced LD, 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. Further details can be found in the APL-2 Investigator's Brochure (Apellis Pharmaceuticals, June 2017).

4.1.2 APL-2

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

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

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

7.1 Inclusion Criteria

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

1. At least 18 years old (inclusive)
2. Diagnosed with PNH (WBC clone >10%)
3. Lactose dehydrogenase ≥2 times the upper limit of normal
4. Screening Ferritin ≥ normal and Total Iron Binding Capacity (TIBC) ≤ LLN based on central lab reference ranges. If a subject is receiving iron supplements at screening, the investigator must ensure that his/her dose has been stable for 8 weeks prior to enrolment and must be maintained throughout the study (see Section 8.4.4)
5. Last transfusion within 12 months prior to screening
6. Platelet count of >30,000/mm^3 at the screening visit
7. Absolute neutrophil count >500/ mm^3 at the screening visit
8. 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
9. Males must agree to use protocol defined methods of contraception and agree to refrain from donating sperm for the duration of the study
10. Vaccination against Neisseria meningitides types A, C, W, Y and B, Streptococcus pneumoniae and Haemophilus influenzae Type B (Hib) either within 2 years prior to Day 1 dosing, or within 14 days after starting treatment with APL-2. Unless documented evidence exists that subjects are non-responders to vaccination as evidenced by titers or display titer levels within acceptable local limits
11. Willing and able to give informed consent

7.1.1 Approved methods of contraception

Approved methods of contraception include: oral contraceptives, intrauterine device, medically acceptable barrier methods (diaphragm or condom), implantable or injectable contraceptives (like 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 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 check-in, as appropriate.

1. Prior eculizumab (Soliris®) treatment
2. Active bacterial infection
3. Hereditary complement deficiency
4. History of bone marrow transplantation
5. Concurrent SAA, defined as currently receiving immunosuppressive therapy for SAA including but not limited to cyclosporin A, tacrolimus, mycophenolate mofetil or anti-thymocyte globulin

8.4.1.3 Alternative prophylactic antibiotics

- Erythromycin 500 mg twice daily
- Azithromycin 500 mg 3 times per week

Erythromycin 500 mg twice daily or Azithromycin 500 mg 3 times per week may be considered as suitable alternatives in subjects who are unable to tolerate penicillin.

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 Rescue antibiotics

Body temperature, vital signs and relevant blood parameters will be monitored regularly throughout the study to assess for signs of infection. The PI 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).

8.4.3 Vaccinations

Vaccination against Neisseria meningitides types A, C, W, Y and B, Streptococcus pneumoniae and Haemophilus influenzae Type B (Hib) is required to participate in this study, either within 2 years prior to Day 1 dosing, or within 14 days after starting treatment with APL-2.

If required i.e. not previously vaccinated subjects will receive vaccinations against Neisseria meningitides types A, C, W, Y and B, Streptococcus pneumoniae and Haemophilus influenzae Type B (Hib). If the subject's first documented *Neisseria meningitidis* vaccine/s are administered at Day 15, a booster (for both vaccinations) should be administered after 2 months. If Pneumococcal vaccination is required, a dose of PCV13 will be administered at Day 15 and a dose of PPSV23 will be administered at least 8 weeks later (unless documented evidence exists that subjects are non-responders to vaccination as evidenced by titers or display titer levels within acceptable local limits). The PI will discuss with the Sponsor in regard to specific patient requirements

8.4.4 Iron Supplements

For subjects receiving iron supplements at the time of APL-2 initiation, iron supplement doses should be maintained stable throughout the study unless iron levels (ferritin and TIBC) increase to unaccepatable levels above ULN during the study. Change in dose of iron supplementation should be discussed with the Sponsor prior to implemntation

8.4.5 Phlebotomy/Venesection for iron overload

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

9. STUDY PROCEDURES

Please see the Study Flow Chart in Section 2 for a summary of the schedule of study participation and procedures. The schedule of visit dates should be established, either, prior to, or at the time of screening allowing subjects an opportunity to assess whether there are likely to be significant conflicts with other activities or planned absences. To the extent possible, subjects will be expected to adhere to the visit schedule and any re-scheduling of visits must be agreed, in advance, with the investigator and sponsor to ensure that the dosing of study medication can continue daily as required.

If a subject's dose is increased beyond 270 mg/day in Part 2B additional site visits will be scheduled for the first 6 weeks of dose increase, alternating with the monthly visits in the protocol.

- Alkaline phosphatase (ALP)
- Lactate dehydrogenase (LD)
- Haptoglobin
- Gamma-glutamyl transpeptidase (GGT)
- Creatine kinase (CK)
- Potassium
- Chloride
- Ferritin
- B12/folate
- Total Iron Binding Capacity (TIBC)

10.1.7.4 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.

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

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

10.1.8 Injection/ Infusion Site and Pump Safety Assessment

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

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

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.

On Day 1 only, a PK sample will be taken pre-dose and at a minimum of 2.5 hours post-dose (or later depending on how long the subject is kept at the clinic). All PK samples on other study days will be collected pre-dose.

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

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 ICH Guidance E6 and local regulations as deemed appropriate.

13.3.3 Subject Information and Consent

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

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

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

13.3.4 Confidentiality

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

13.3.5 ClinicalTrials.gov

This study has been 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 PI reserves the right to discontinue dosing subjects at any time for safety reasons.

13.4 Data Handling and Record Keeping

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

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