Protocol No.: APL2-CP-PNH-204

A Phase Ib, Open Label, Multiple Ascending Dose, Pilot Study to Assess the Safety, Preliminary Efficacy and Pharmacokinetics of Subcutaneously Administered APL-2 in Subjects with Paroxysmal Nocturnal Hemoglobinuria (PNH). – PADDOCK –

Phase: Ib

Version: Protocol Amendment 8.0

Date: 25 October 2018

1. SYNOPSIS

Protocol Number

APL2-CP-PNH-204

Official Tittle

A Phase Ib, Open Label, Multiple Ascending Dose, Pilot Study to Assess the Safety, Preliminary Efficacy and Pharmacokinetics of Subcutaneously Administered APL-2 in Subjects with Paroxysmal Nocturnal Hemoglobinuria (PNH). – PADDOCK –

Protocol Version and Date

Protocol Amendment 8.0

FINAL 25 October 2018

Compound

APL-2

Study Phase and Type

Phase Ib. Open-label, evidence of activity, safety, tolerability, pharmacokinetics (PK), multiple ascending dose, pilot study.

Study Objectives

The objectives of the study are to assess the safety, tolerability, preliminary efficacy and PK of multiple subcutaneous (SC) doses of APL-2 in subjects with paroxysmal nocturnal hemoglobinuria (PNH) who have not received treatment with eculizumab in the past.

An exploratory objective of the study is to assess the pharmacodynamics (PD) of 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) and at least 18 years old
- have a diagnosis of PNH

Number of Subjects

The study is planned to enrol approximately 23 subjects across two cohorts. Cohort 1 will include 3 subjects. Cohort 2 will include sufficient subjects to ensure that up to 20 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 Principal Investigator (PI) and the Sponsor to repeat a dose level or to study an additional dose level.

Inclusion Criteria

At Screening (unless otherwise specified)

- Male or female
- At least 18 years old (inclusive)
- Weigh >40 kg and have a body mass index (BMI) ≤38.0 kg/m^2
- Diagnosed with PNH (white blood cell (WBC) clone >10%)
- Lactose dehydrogenase (LD) ≥2 times the upper limit of normal
- Ferritin ≥ lower limit of normal (LLN) as defined by the central laboratory and Total Iron Binding Capacity (TIBC) ≤ upper limit of normal (ULN) 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 9.4.5)
- Last transfusion within 12 months prior to screening
- Platelet count of >30,000/mm^3
- Absolute neutrophil count >500/µL
- 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 and 90 days after their last dose of study drug
- Males must agree to use protocol defined methods of contraception and agree to refrain from donating sperm for the duration of the study and 90 days after their last dose of study drug
- Vaccination against *Neisseria 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 either within 2 years prior to Day 1 dosing, OR 14 days after starting treatment with APL-2.
- Willing and able to give informed consent

Exclusion Criteria

- Prior eculizumab (Soliris)® treatment
- Active bacterial infection
- Active infection with hepatitis B virus (HBV), hepatitis C virus

(HCV) or human immunodeficiency virus (HIV)

- 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
- Evidence of QTcF prolongation defined as >450 ms for males and >470 ms for females at screening.
- Breast-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
- Number of red blood cell (RBC) transfusions per month

Exploratory PD markers include:

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

Planned Dose Levels

Planned doses will be as follows:

	SC dose
Cohort 1	180 mg / day
Cohort 2	Starting dose 270 mg / day
Cohort 2	Intra-subject escalation Up to 360 mg/day

The dose for Cohort 2 was determined based on cumulative safety, PK, and PD data from Cohort 1.

Dose escalation decisions will be agreed by a Safety Monitoring Committee (SMC), based on the safety and pharmacology results from the prior cohort(s). SMC review of cumulative data will occur approximately monthly.

Study Design

This is a Phase Ib, open-label, multiple ascending dose, pilot study in patients with PNH who have not received eculizumab (Soliris®) in the past. Two cohorts of subjects are planned for evaluation. Cohort 1 will include 3 subjects and Cohort 2 will include up to 20 subjects who complete Part 1 (28 days of dosing). Subjects may participate in more than one cohort.

Safety will be assessed throughout the study; serial blood and urine samples will be collected for these assessments. Blood samples will be collected for the assessment of APL-2 PK. Additional samples for assessment of PD will also be collected.

The study will consist of four parts;

- Part 1: subjects will receive APL-2 for 28 days.
- Part 2A: subjects may continue to receive APL-2 for a further 56 days if there is evidence of perceived clinical benefit following review of available safety, PK and PD data by the investigator and sponsor
- Part 2B: subjects may continue to receive daily APL-2 treatment for up to 364 days if there is ongoing evidence of clinical benefit following review of the available safety, PK and PD data.
- Part 3: Safety follow up (if applicable; subjects may also transition into an open-label extension study to continue

treatment with APL-2 after the completion of Part 2B)

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. During Part 1, the first 3 daily SC doses of APL-2 (Day 1 to 3) as well as doses on Day 8, 15 and 22 will be administered at the clinical site. From Day 4 to Day 28 daily doses of APL-2 will be administered off-site by a trained study nurse or self-administered by the subject, at the subject's home, workplace, or other location convenient to the subject with the exception of those days where dosing is at the clinical site (see above). Following ongoing review of available safety, PK and PD data by the investigator and sponsor, subjects showing evidence of perceived clinical benefit may progress to Part 2A and then to Part 2B of the study and continue to receive daily doses of APL-2 until Day 84 and then until Day 364. Doses will be administered off-site by a study nurse or self-administered by the subject, at the subject's home, workplace, or other 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 at the clinical site. After the conclusion of the treatment period (Day 364), subjects will 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 Flow Chart in Section 3.

Cohort 2 will not be initiated until all subjects in Cohort 1 have reached the Day 29 visit and the SMC has reviewed emerging safety and efficacy data and determined that, at the initial dose, APL-2 has an acceptable safety and tolerability profile.

Interim PK and PD analyses may be performed to reconsider the sampling time points as the study progresses.

Subjects who complete Part 2B will be eligible to transition into an open-label extension study (Study APL2-307) in order to continue to receive treatment with APL-2. Subjects who elect to transition into Study APL2-307 will not complete Part 3 of this study.

The planned length of participation in the study for each subject in Cohort 2 is a maximum of 444 days (14.5 months) from Day -30 through completion of the Day 414 Exit visit procedures).

The study is planned to take place over approximately 24 months (from screening of Cohort 1 through completion of Cohort 2).

Some subjects who complete Part 2B and wish to transition into the open-label extension study may be required to dose beyond the planned conclusion of Part 2B (Day 364) in this study. This study utilizes an acetate buffered mannitol formulation of APL-2. The open-label extension study will utilize an alternate acetate buffered sorbitol formulation. Some subjects may complete Part 2B of this study before there is sufficient availability of the alternate acetate buffered sorbitol formulation to conduct Study APL2-307. Subjects who complete Part 2B prior to Study APL2-307 being open for enrollment to subjects in this study may continue dosing with the acetate buffered mannitol formulation under this protocol (Part 2C), until the extension study is open to them for enrollment. These subjects will continue to receive their current APL-2 dose and regimen and will return to the site for visits at bi-monthly intervals until entry into the extension study is possible. Data obtained from subjects who participate in Part 2C will not be included in endpoint assessment and will be only listed.

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3. STUDY FLOW CHART

Study Period	Screen		Part 1- Treatment (Daily from Day 1 to Day 28)									
Study Week	-4	-2	1				2		3		4	
Study Day	-30	-14	1	2	3	4 to 7	8	9 to 14	15	16 to 21	22	23 to 28
Informed Consent	x											
Demographics	x											
Medical, transfusion, vaccination and thrombosis history	x											
Vaccination. A									x			
Review entry criteria			x									
Preventive antibiotic. B			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**	**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	x
Vital sign measurements. G	x		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 **(I)**	x	x		x				x	
Anti-APL-2 Ab assay			x						x			
Hematology and chemistry. **J**	x		x				x		x		x	x **(J)**
Coagulation profile **P**	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	
Serology (HIV, HBsAg and HCV.) **K**	x											
Pregnancy (B-human chorionic gonadotropin)	x											
Urine pregnancy test. L			x				x		x		x	
FACIT fatigue Scale			x						x			
Adverse events M			x	x	x	x	x	X	x	X	x	x
Thrombosis record (MAVE).			x	x	x	x	x	X	x	X	x	x

See notes 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	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. **J**		X		X		X		X		X	
Coagulation profile **P**		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. L		X		X		X		X		X	
FACIT fatigue Scale		X				X				X	
Adverse events M		X	X	X	X	X	X	X	X	X	X
Thrombosis record (MAVE)		X	X	X	X	X	X	X	X	X	X

See footnotes below continuation flow chart

Study Period	**Part 2B - Treatment (Daily from Day 85 to Day 364) (N)**											
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
Informed Consent	X											
Review entry criteria	X											
Vaccination. A	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. **J**	X		X		X		X		X		X	
Coagulation profile **P**	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. L	X		X		X		X		X		X	
FACIT fatigue Scale	X				X				X			
Adverse events M	X	X	X	X	X	X	X	X	X	X	X	X
Thrombosis record (MAVE)	X	X	X	X	X	X	X	X	X	X	X	X

See footnotes below continuation flow chart

Study Period	**Part 2B - Treatment (Daily from Day 85 to Day 364) … continued (N) (Q)**								**Part 3 – Follow-up and Exit· (O)(Q)**			
Study Week	37 to 40		41 to 44		45 to 48		49 to 52		53	55	57	60
Study Day	253	254 to 280	281	282 to 308	309	310 to 336	337	338 to 364	365	379	393	414
Informed Consent												
Review entry criteria												
Preventive antibiotic. B	X	X	X	X	X	X	X	X	X	X		
Physical examination. C	X						X		X			X
12-lead electrocardiogram. D	X		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	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	X	X
Blood. I	X		X		X		X		X	X	X	X
Pharmacokinetics. **I**	X		X		X		X		X	X	X	X
Anti-APL-2 Ab assay	X				X				X			X
Hematology and chemistry. **J**	X		X		X		X		X	X	X	X
Coagulation profile **P**	X		X		X		X		X	X	X	X
Complement profile (C3, CH50 and AP50)	X		X		X		X		X	X	X	X
Flow cytometry for PNH/C3 deposition	X		X		X		X		X	X	X	X
Plasma Hb	X		X		X		X		X	X	X	X
Urine pregnancy test. L	X		X		X		X		X		X	X
FACIT fatigue Scale	X				X				X		X	X
Adverse events M	X	X	X	X	X	X	X	X	X	X	X	X
Thrombosis record (MAVE)	X	X	X	X	X	X	X	X	X	X	X	X

See study flow chart footnotes on next page

FOOTNOTES:

A. At screening the vaccination history will be obtained from the subject. If required i.e. not previously vaccinated subjects will receive vaccinations against Neisseria meningitides types A, C, W, Y and B (administered as two vaccinations), 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 at least 2 months later (Day 85). 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 (Day 85).

B. Preventive antibiotics will be prescribed from Day 1. Antibiotics will be taken from Day 1 until 14 days after the final dose of APL-2. Specifically:

- Day 1 to Day 14: Ciprofloxacin 500 mg twice daily to commence after collection of the 2.5h post dose PK sample
- Day 15 onwards: Penicillin V 500 mg twice daily.

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. N.B. On Day 1 the ECG must be performed BEFORE administration of the first dose of Ciprofloxacin.

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 continue APL-2 administration past this point.

F. Injection site assessment will be performed within 30 minutes after APL-2 administration. Ambulatory syringe infusion pump training will include instructions to report any injection site reaction to the PI.

G. If APL-2 is administered by a study nurse or other research study staff, vital signs will be measured within 2 hours prior to dosing and within 30 minutes after dosing. If APL-2 is self-administered, pre- and post-dose vital signs will not be measured.

H. Reserved – See note E.

I. If done on a dosing day, blood samples will be taken pre-dose with the exception that on Day 1 only a pharmacokinetic sample will be taken pre-dose and at a minimum of 2.5 hours post-dose or immediately prior to discharge from the clinic (if subject is kept at the clinic longer than 2.5 hours).

J. On Days 23 through 28, a serum chemistry sample may be obtained but LD assays only will be performed and reported. If a sufficient reduction in LD is observed prior to Day 22 these additional samples may not be required and this will be confirmed on an individual subject basis by the sponsor

K. Absence of HIV, HBV, and HCV infection will be confirmed prior to APL-2 administration. If the HBsAg test yields a positive result, a negative HBV DNA test result must be obtained and prophylactic antiviral therapy must be commenced prior to APL-2 administration and continue until two weeks after the final dose of APL-2 to minimize the potential risk of HBV activation.

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

M. Ambulatory syringe infusion pump training will include instructions to report any adverse events to the PI.

N. If dose is increased during Part 2B, subjects will come back to the clinical site for safety visits every other week (instead of monthly) for the first 6 weeks of the dose change. These visits will alternate with the monthly visits and should be recorded as unscheduled visits. The same procedures listed under the monthly visits will be performed.

O. Subjects who discontinue dosing at any time during part 1, 2A or 2B, will move directly into Part 3 for safety follow up visits.

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

Q. Subjects who complete Part 2B will be eligible to transition into an open-label extension study (Study APL2-307) in order to continue to receive treatment with APL-2. Subjects who elect to transition into Study APL2-307 will not complete Part 3 of this study, but must complete the Day 365 visit procedures (the first visit of Part 3). The Day 365 visit will also be the first visit of the extension study. If Study APL2-307 is not open to enroll subjects from this study, subjects may continue dosing with APL-2 beyond Part 2B in Part 2C of this study. Details regarding procedures for dosing beyond Part 2B are provided in Appendix 1 (Section 16).

4. ABBREVIATIONS

ADL	Activities of daily living
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BMI	Body mass index
BUN	Blood urea nitrogen
°C	Degrees Celsius
CK	Creatine kinase
CRF	Case report form
CS	Clinically significant abnormality
ECG	Electrocardiogram
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Unites States Foods and Drug Administration
g	Gram(s)
GCP	Good clinical practice
GGT	Gamma-glutamyl transpeptidase
GLP	Good laboratory practice
Hb	Haemoglobin
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
hERG	Human ether-à-go-go-related gene
Hib	*Haemophilus influenzae* Type B (vaccine)
HIV	Human immunodeficiency virus
HSA	Human serum albumin
IB	Investigator's brochure
ICH	International Conference on Harmonization
IV	Intravenous
kg	Kilogram(s)
L	Litre(s)
LD	Lactate dehydrogenase
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
µM	Micromolar; micromoles/L
NCS	Not clinically significant
NOEL	No observed effect level
NOAEL	No observed adverse effect level
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
ULN	Upper Limit of Normal
WBC	White blood cell
WHO	World Health Organization
WOCBP	Woman of Child-Bearing Potential

5. INTRODUCTION

5.1 Background

This study is being conducted as part of a series of studies for the clinical development of APL-2. The 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).

5.1.1 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, 2015).

5.1.2 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 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).

5.1.2.1 Nonclinical Data

5.1.2.1.1 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 RBC from complement-mediated lysis and also prevent 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. Based upon the available *ex vivo* and clinical data, the efficacious dose for humans has been estimated to be between 2 mg/kg/d and 4 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 human serum albumin (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.

5.1.2.1.2 Pharmacokinetics

Pharmacokinetics and toxicokinetics have been performed in rabbits and monkeys administered APL-2 by intravenous (IV) or SC routes. Excellent bioavailability (approximately 85%) and $t_{½}$s in the range of 6 to 8 days were obtained with both routes of administration in Cynomolgus monkeys. $T_{½}$s in rabbits were shorter, ranging from 2 to 3 days.

5.1.2.1.3 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 in cynomolgus monkeys has recently completed its *in-life* phase and final data from the 3-month interim necropsy and draft data from the final 9-month necropsy 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 most of these 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.

APL-2 did not induce genotoxicity in a bacterial reverse-mutation assay (Ames test) nor in an *in vitro* mammalian cell micronucleus test using TK6 cells (proficient p53 human lymphocytes). During *in vivo* assessments, APL-2 exhibited no clastogenic effect in the mouse micronucleus model.

Pharmacokinetics 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. The long half-life of APL-2 resulted in a slowly increasing serum concentration over time that reached a steady state plateau after a few weeks of dosing. APL-2 was mildly antigenic in rabbits; however, the response was concluded to be caused by the PEG40 chain in both molecules and it did not affect serum concentrations of APL-2. APL-2 and PEG40 were not immunologic in monkeys.

In 28-day GLP rabbit and monkey studies 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 0.25, 1, 3, 7, 28 or 140 mg/kg/d. APL-2 was well tolerated, with no mortality observed. A no-observable-effect level (NOEL) was approximated to be 3 mg/kg/d and the no-observable-adverse-event-effect level (NOAEL) was concluded to be ≥7 mg/kg/d in both species.

Observations were generally consistent between both species. General observations include dose-dependent inflammatory cell infiltrates at sites of injection comprised of lymphocytes, plasma cells or granulocytes, as well as frequent multinucleated cells. Additionally, dose-dependent macrophage vacuolation was observed in multiple tissues, which is a known adaptive change attributable to the administration of PEG.

Observations at the 28 and 140 mg/kg/d dose levels included a dose-dependent increase in RBC parameters (RBC counts, hematocrit, and Hb), reticulocyte counts, and partial activated thromboplastin time, and a dose-dependent decrease in WCBs, fibrinogen levels and differential lymphocyte counts. Some but not all of these observations resolved themselves by the end of a 4 week recovery phase. Observations at the two higher doses also included dose-dependent kidney tubular vacuolation and degeneration that were not reversible after a 4 week recovery phase. These kidney-related findings are also a known change attributed to PEG.

The draft data, including full histopathological assessment, from 9 months of daily SC administration in the cynomolgus monkey and 6 months of daily SC administration in the New Zealand white rabbit both concluded that the main toxicological findings are 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 final necropsy in the monkey study.

Similar to 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 necropsy in the chronic 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 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.

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

5.1.2.2 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 is a single ascending dose study (Study APL-CP0713-1) and the second is 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-CP-PNH-204) and a study in patients who are receiving treatment with eculizumab (APL-CP0514).

5.1.2.2.1 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 1,440 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.

5.1.2.2.2 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. One subject who received APL-2 180 mg had increased ALT and AST levels on Day 15. The findings were considered by the investigator to be clinically significant and therefore were reported as AEs. Values for both parameters returned to within normal limits by Day 29 despite continued dosing with APL-2 between Day 15 and Day 29. 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. 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.

5.1.2.2.3 APL-2 in patients with PNH receiving eculizumab

This study is an ongoing initial exploration of APL-2 in patients with PNH who are receiving treatment with eculizumab. The study is comprised of 3 cohorts with two subjects per cohort, and one cohort of six subjects. Cohort 1 to 3 have been completed and Cohort 4 is ongoing. To date treatment with APL-2 270 mg/day has been well-tolerated for at least two months and has provided clinical benefit in subjects with PNH as an add-on to eculizumab. Based on the emerging data, dosing will continue for up to 364 days.

5.2 Rationale

5.2.1 Purpose of the Study

This study will be the initial exploration of APL-2 in patients with PNH that have not received treatment with eculizumab in the past. The assessments of safety, tolerability, preliminary efficacy, PK, and PD following administration of multiples doses of APL-2 will guide decisions to further develop the drug.

5.2.2 Dose Selection

APL-2 appeared to be well tolerated in a panel of standard animal toxicology studies and initial clinical testing in healthy volunteers. A population-based PK model was built from available single-dose and repeated-dose clinical data and used to predicted C_{max} and AUC values for future doses. Monkey and human C_{max} and AUC data were used to compare APL-2 exposures between species when necessary, although for chronic dosing, the C_{max} (which is the APL-2 concentration at steady state in a daily dosing regimen) is the primary parameter to compare exposure (AUC becomes approximately the integration of C_{max} in cases where dosing is much longer than the $T_{1/2}$ of the drug).

In the nonclinical toxicology studies described in the Investigator's Brochure, the NOEL in both monkeys and rabbits was determined to be approximately 3 mg/kg/d in a 28 day study. A NOAEL between 7 mg/kg/d and 28 mg/kg/d in monkeys was established during a 9-month GLP study CCI [redacted]. Monkeys are considered the most relevant and pivotal species since APL-2 is only pharmacologically active as a complement inhibitor in primates. Additionally, compared with the PK parameters observed in rabbits (C_{max}, $t_{1/2}$, and AUCs), the PK parameters observed in monkeys correlate better with PK data obtained from the clinical studies APL-CP0713-1 and APL-CP1014.

The available 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: Comparison of PK parameters obtained from the IND-enabling toxicology study and clinical trials in healthy volunteers. All values reported as arithmetic means.

	Notes	Dose (mg/kg)	C_{max} (µg/mL)	C_{max} % NOAEL
Monkey	NOAEL; Study CCI [redacted]	7	1087	--
Human	45 mg single dose; APL-CP0713-1	0.6[a]	7	0.6%
	90 mg single dose; APL-CP0713-1	1.3[a]	16	1.4%
	180 mg single dose; APL-CP0713-1	2.6[a]	29	2.6%
	360 mg single dose; APL-CP0713-1	5.1[a]	74	6.8%
	720 mg single dose; APL-CP0713-1	10.3[a]	139	13%
	1440 mg single dose; APL-CP0713-1	20.6[a]	252	23%
	30 mg/d x 28 days; APL-CP1014	0.43[a]	77	7%
	90 mg/d x 28 days; APL-CP1014	1.29[a]	259	24%
	180 mg/d x 28 days; APL-CP1014	2.6[a]	473	43%
	270 mg/d x 28 days; APL-CP1014	3.9[a]	670	62%
	360 mg/d PREDICTED	5.14	790	73%

The toxicological data accumulated from the animal studies were used to guide dose selection during the Phase I single ascending dose and multiple ascending dose studies in healthy volunteers (protocols

APL-CP0713-1 and APL-CP1014 respectively). In particular, the highest doses were selected based on exposure predicted by the PK model and compared with the exposures measured at the NOAEL in monkeys.

The starting dose for this trial will not exceed the highest dose tested in the multiple ascending dose study in healthy volunteers, which was found to be well-tolerated. At the time of initiation of this study, this highest dose was 180 mg/d, which corresponds to an exposure of approximately 50% of the NOAEL in monkeys, but ongoing trials might provide additional safety data to support a higher starting dose. 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) so a lower starting dose cannot be justified in this patient trial.

The dose of the next cohort will be escalated by up to 50%. For example, if the dose of the first cohort is 180 mg/d, the starting dose of the following cohort will not exceed 270 mg/d. The dose selected for any cohort or 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.

5.3 Risk/Benefit

A number of safety monitoring practices are required by this protocol (i.e. physical examination, vital signs, 12-lead ECG, hematology, serum chemistry, urinalysis, coagulation, prompt reporting of pre-defined AEs of special interest, and AE questioning) in order to protect the subjects' safety.

The volume of blood planned for collection from each subject over the course of the study (see Section 11.4) will be limited to approximately 580 mL, in order to minimize the impact on the overall health of these anemic subjects. If dose is increased during part 2B, additional blood draws will be scheduled requiring an additional blood volume of 45 mL.

Systemic complement inhibition might predispose individuals to infections caused by encapsulated organisms, including *Streptococcus pneumoniae*, *Neisseria meningitides*, and *Haemophilus influenza*. Prophylactic antibiotic therapy (ciprofloxacin 500 mg BID) will be prescribed to all subjects from Day 1 (commencing after first administration of APL-2 and the subsequent post-dose PK sample and ECG) to Day 14. At Day 15 all subjects will discontinue treatment with ciprofloxacin and receive vaccinations, if required, against *Streptococcus pneumoniae*, *Neisseria meningitides A, C, W, Y and B*, and *Haemophilus influenza*. Prophylactic antibiotic therapy (penicillin V 500 mg twice a day) will be prescribed to all subjects from Day 15 and will be taken by subjects until 14 days after the final dose of APL-2 to minimize potential infection risk. Body temperature and vital signs will be monitored daily 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 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 9.4 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 500 mg twice daily (see Section 9.4 for details) if there is evidence of penicillin-related intolerability (such as nausea and diarrhea).

There is a potential health benefit for trial participants from receipt of study drug. At the proposed dose levels APL-2 we observed a significant decrease in complement mediated hemolytic activity in all APL-2 treated subjects in our 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. In addition, in both studies in subjects with PNH (See Section 5.1.2.2), ongoing treatment with APL-2 270 mg/day has been well-tolerated for at least 28 days and up to 5 months and has provided clinical benefit to subjects either alone or as an add-on to eculizumab. Based on this data we propose to continue to administer APL-2 to PNH patients for up to 364 days (1 year). See Planned Dose Levels and Dosing Schedule in Section 9.3.2.

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

Details regarding the dosing regimen and administration of APL-2 are provided in Section 9.3. Subjects should be instructed to take their APL-2 treatment as prescribed, and to contact the investigator immediately for guidance in the event of any missed doses. Discontinuation with APL-2 or non-compliance with the prescribed dose regimen may lead to the potential for an increased risk for serious hemolysis. The Sponsor's medical monitor should be contacted before interrupting or discontinuing treatment with APL-2.

If efficacious and safe, APL-2 is expected to continue to improve Hb levels and reduce transfusion dependency in these patients throughout the treatment period of 364 days. Individual patient data will continue to be reviewed on an ongoing basis to understand if there is a health benefit in these individuals during the treatment period. 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. If a benefit is observed an extension study will be considered and will be submitted as a protocol amendment or as a follow-up study.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

The objectives of the study are to assess safety, tolerability, preliminary efficacy and PK of multiple SC doses of APL-2 in subjects with paroxysmal nocturnal hemoglobinuria (PNH) who have not received treatment with eculizumab (Soliris)® in the past.

An exploratory objective of the study is to assess the pharmacodynamics (PD) of multiple SC doses of APL-2 when administered to PNH patients. See "Study Endpoints" in Section 6.2.

6.2 Study 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 Hb

Secondary endpoints:

- APL-2 plasma concentrations (and PK parameters as appropriate)
- Change from baseline in FACIT Fatigue Scale score
- Change from baseline in reticulocyte count
- Number of RBC transfusions per month

Exploratory PD markers include:

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

7. STUDY DESIGN

This is a Phase Ib, open-label, multiple ascending dose, pilot study in patients with PNH who have not received eculizumab (Soliris)® in the past. The study is planned to enroll approximately 23 subjects across two cohorts. Cohort 1 will include 3 subjects. Cohort 2 will include up to 20 subjects. Subjects may participate in more than one cohort. Cohort 1 has completed.

Safety will be assessed throughout the study; serial blood and urine samples will be collected for these assessments. Blood samples will be collected for the assessment of APL-2 PK. Additional samples for assessment of PD will also be collected.

The study will consist of three parts;

- Part 1: Up to 20 subjects in cohort 2 will receive APL-2 for 28 days.
- Part 2A: Following review of available safety, PK and PD data by the investigator and sponsor, subjects showing evidence of perceived 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 perceived 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 If applicable; subjects may also transition into an open-extension study to continue treatment with APL-2 after the completion of Part 2B, or may continue treatment with APL-2 in Part 2C if enrollment into the extension study is not yet available (see Appendix 1, Section 16). Subjects that transition to either the extension study or Part 2C must complete the Day 365 visit procedures for this study. For these subjects, the Day 365 visit will also be the first visit of the extension study or Part 2C.

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. During Part 1, the first 3 daily SC doses of APL-2 (Day 1 to 3) as well as doses on Day 8, 15 and 22 will be administered at the clinical site. From Day 4 to Day 28 daily doses of APL-2 will be administered off-site by a study nurse or self-administered by the subject, at the subject's home, workplace, or other location convenient to the subject with the exception of those days where dosing is at the clinical site (see above). 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 administered off-site by a study nurse or self-administered by the subject, at the subject's home, workplace, or other 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 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. 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 3.

Subjects who complete Part 2B will be eligible to transition into an open-label extension study (Study APL2-307) in order to continue to receive treatment with APL-2. Subjects who elect to transition into Study APL2-307 will not complete Part 3 of this study.

Cohort 2 will not be initiated until all subjects in Cohort 1 have reached the Day 29 visit and the SMC has reviewed emerging safety and efficacy data and determined that, at the initial dose, APL-2 has an acceptable safety and tolerability profile.

The planned length of participation in the study for each subject is a maximum of 444 days (from Day –30 through completion of the Day 414 Exit visit procedures). The study is planned to take place over approximately 24 months (from screening of Cohort 1 through completion of Cohort 2). Interim PK and PD analyses may be performed to reconsider the sampling time points as the study progresses.

Some subjects who complete Part 2B and wish to transition into the open-label extension study may be required to dose beyond the planned conclusion of Part 2B (Day 364) in this study. This study utilizes an acetate buffered mannitol formulation of APL-2. The open-label extension study will utilize an alternate acetate buffered sorbitol formulation. Some subjects may complete Part 2B of this study

before there is sufficient availability of the alternate acetate buffered sorbitol formulation to conduct Study APL2-307. Subjects who complete Part 2B prior to Study APL2-307 being open for enrollment to subjects in this study may continue dosing with the acetate buffered mannitol formulation under this protocol until the extension study is open to them for enrollment. Subjects that participate in Part 2C must complete the Day 365 visit procedures as outlined in the schedule of assessments, with the addition of APL-2 dosing and dispensation. The Day 365 visit that is the first visit of Part 3 will also be the first visit of Part 2C. These subjects will continue their APL-2 dose and regimen and will return to the site for visits at bi-monthly intervals until the extension study is open to them. Details regarding procedures for dosing beyond Part 2B are provided in Appendix 1 (Section 16).

8. SUBJECT SELECTION

The study is planned to enroll approximately 23 subjects, with 3 subjects in Cohort 1 and sufficient subjects in Cohort 2 for up to 20 subjects to complete at least 28 days of dosing. Additional cohorts may be enrolled if it is deemed appropriate by the PI (or designee) and the Sponsor in consultation with the SMC to repeat a dose level or to study an intermediate dose level.

8.1 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. Male or Female
2. At least 18 years old (inclusive)
3. Weigh >40 Kg and have a BMI ≤38.0 kg/m^2
4. Diagnosed with PNH (WBC clone >10%)
5. Lactose dehydrogenase ≥2 times the upper limit of normal
6. Ferritin ≥ lower limit of normal (LLN) as defined by the central laboratory and Total Iron Binding Capacity (TIBC) ≤ upper limit of normal (ULN) 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
7. Last transfusion within 12 months prior to screening
8. Platelet count of >30,000/mm^3
9. Absolute neutrophil count >500/µL
10. 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 and 90 days after their last dose of study drug
11. Males must agree to use protocol defined methods of contraception and agree to refrain from donating sperm for the duration of the study and 90 days after their last dose of study drug
12. 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 14 days after starting treatment with APL-2.

13. Willing and able to give informed consent

8.1.1 Approved methods of contraception

Approved methods of contraception include: abstinence, 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 and 90 days after their last dose of study drug.

8.2 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. Active infection with hepatitis B virus (HBV), hepatitis C virus (HCV) or human immunodeficiency virus (HIV)
4. Hereditary complement deficiency
5. History of bone marrow transplantation
6. Concurrent SAA, defined as currently receiving immunosuppressive therapy for SAA including but not limited to cyclosporin A, tacrolimus, mycophenolate mofetil or anti-thymocyte globulin
7. Participation in any other investigational drug trial or exposure to other investigational agent, device or procedure within 30 days
8. Evidence of QTcF prolongation defined as >450 ms for males and >470 ms for females at screening
9. Breast-feeding women
10. History of meningococcal disease

9. STUDY TREATMENTS

9.1 Allocation to Treatment

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

9.2 Blinding

None; this is an open-label study.

9.3 Treatments Administered

Sterile solutions of APL-2 up to 150 mg/mL in 5% dextrose or in acetate-buffered mannitol or in acetate-buffered sorbitol, administered SC.

9.3.1 Drug supplies

9.3.1.1 Identity of Investigational Products

APL-2 will be supplied as a sterile solution of APL-2 in 5% dextrose or as a sterile solution of APL-2 in acetate-buffered mannitol or in acetate-buffered sorbitol, at concentrations of up to 150 mg/mL, supplied in stoppered glass vials.

9.3.1.2 Study Supplies

The Sponsor will supply sufficient quantities of APL-2 drug product to allow completion of this study. The lot numbers, manufacture dates, and expiration dates of the drugs supplied will be recorded in the final report. The Sponsor will also supply needles, syringes, and ambulatory syringe infusion pumps (e.g. Crono Super PID) as required. APL-2 in 5% dextrose solution should be stored at -20°C. APL-2 acetate-buffered mannitol solution and APL-2 acetate-buffered sorbitol solution should be stored at 2-8°C.

A pharmacist or appropriately qualified designated person will be responsible for storing the APL-2 appropriately; dispensing the vials of APL-2 to the subject, study nurse, or other study personnel, and for maintaining accountability records.

9.3.1.3 Accountability

Records will be made of the receipt and dispensing of APL-2 for administration both on and off-site.

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

9.3.2 Planned Dose Levels and Dosing Schedule

Starting on Day 1 (Visit 3), subjects will receive SC APL-2 daily for up to 364 days at the corresponding dose for their cohort.

Planned doses will be as follows:

Cohort	Planned dosing schedule (Amendment 4)
1	180 mg/day from Day 1 to Day 28
2	270 mg/day (up to 360 mg/day) from Day 1 to Day 364*

* The dose may be increased up to 360 mg/day if the clinical response is sub-optimal. The volume to be administered will depend on the final concentration provided and may be administered as either 1 or 2 bolus SC injections or as a SC infusion.

The starting dose for Cohort 2 was determined based on safety, PK, and PD data from Cohort 1.

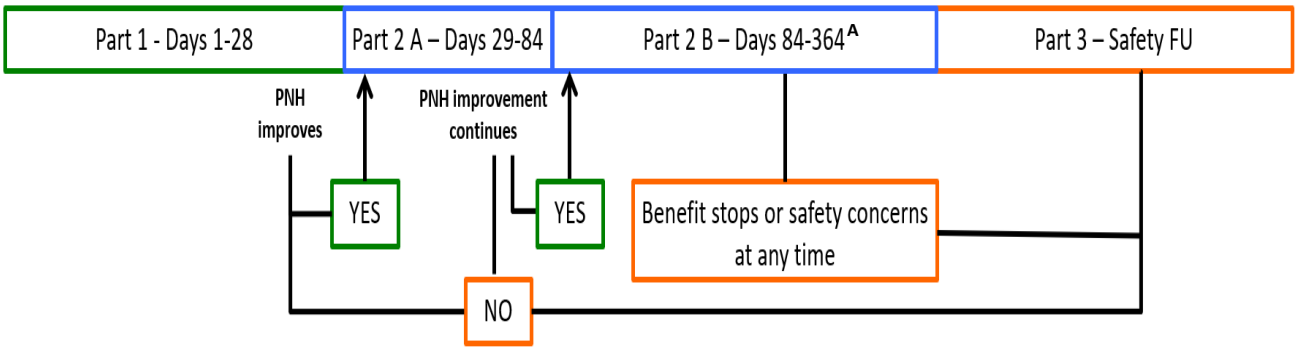
Repeat of a cohort or the addition of another dose level (i.e. another cohort) will be agreed by the SMC based on evidence of clinical benefit and review of available safety data from prior and current

cohort(s). 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 a cohort. The dose selected for any cohort or 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.

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. LD levels will be measured weekly until Day 22 and may be measured daily between Day 23 and Day 28. On Day 28, 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 (Day 29 to 84). On Day 84, subjects concluded to continue to benefit from the treatment (as determined by the Investigator and sponsor after reviewing the available data) will automatically enter into Part 2B and will continue treatment up until Day 364. Following Part 2B, subjects will either transition into the open-label extension study APL2-307, or will complete the Part 3 safety follow up procedures. Subjects who complete Part 2B prior to Study APL2-307 being open for enrollment to subjects in this study may continue to receive treatment with APL-2 as detailed in Appendix 1 (Section 16). Subjects that transition to either the extension study or Part 2C must complete the Day 365 visit procedures for this study. For these subjects, the Day 365 visit will also be the first visit of the extension study or Part 2C.

The first SMC meeting was scheduled once all subjects in Cohort 1 reached Day 28, and subsequent SMC meetings were held, and will continue to be held, at regular intervals throughout the study.

Continuation of treatment – Decision scheme



[A] Following Part 2B, subjects will either transition into the open-label extension study, APL2-307, or will complete the Part 3 safety follow up procedures. Subjects who complete Part 2B prior to Study APL2-307 being open for enrollment to subjects in this study may continue to receive treatment with APL-2 as detailed in Appendix 1 (Section 16). Subjects that transition to either the extension study or Part 2C must complete the Day 365 visit procedures for this study. For these subjects, the Day 365 visit will also be the first visit of the extension study or Part 2C.

9.3.3 Drug Administration

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 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. 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

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.

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

9.3.4 Additional Dose Levels

Repeat of any cohort or the addition of intermediate dose level may be added, as determined by the SMC, depending on the safety and efficacy results from the prior cohort(s).

9.4 Concomitant Medications

9.4.1 Prophylactic antibiotics

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

9.4.1.1 Primary prophylactic antibiotic Day 1-14

- Ciprofloxacin 500 mg twice daily, initial administration on Day 1 will take place after the initial APL-2 dosing and after the post dose ECG has been taken

9.4.1.2 Primary prophylactic antibiotic Day 15 – 2 weeks after last dose

- 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.

9.4.1.3 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 a suitable alternative in subjects who are unable to tolerate penicillin.

Treatment should be switched 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.

9.4.2 Rescue antibiotics

Body temperature and vital signs will be monitored daily 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).

9.4.3 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 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 at least 2 months later (Day 85). 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 (Day 85).

9.4.4 Prophylactic antivirals

Prophylactic antiviral therapy will be prescribed to all HBsAg-positive subjects to minimize the potential risk of HBV activation. Prophylactic antivirals will be initiated at least two weeks prior to initiation of APL-2 dosing and continue until 2 weeks after the last dose.

9.4.5 Iron Supplements

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

10. STUDY PROCEDURES

Please see the Study Flow Chart in Section 3 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. i.e. subjects will

return to the clinical site every two weeks for 6 weeks. These will be scheduled by the investigator and the same procedures as the monthly visits will be performed. These visits will be recorded as unscheduled visits.

10.1 Screening

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 14.3.3). Subjects will have to meet all eligibility criteria before being enrolled into the study (see Section 8).

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 3.

10.2 Part 1 - Treatment Period – (Days 1 to 28)

Subjects will receive daily SC doses of APL-2 on Days 1 to 28. APL-2 will be administered at the clinical site by study personnel or off-site at the subject's home, workplace, or other location convenient to the subject by a trained study nurse or will be self-administered by the subject.

10.2.1 On Site Administration (Day 1 to Day 3 and Days 8, 15 and 22)

The first 3 daily SC doses of APL-2 (Day 1 to 3) as well as doses on 8, 15 and 22 will be administered at the clinical site. Subjects will remain in the clinic for at least 2.5 hours after receiving the first dose of APL-2 on Day 1.

If required subjects will receive vaccinations on Day 15 with boosters scheduled appropriately. On day 15, ciprofloxacin will be discontinued and penicillin V commenced.

Blood samples for laboratory analysis, PK/PD, and antigenicity will be taken during site visits as outlined in the Study Flow Chart in Section 3.

Specific procedures for each visit are listed in the Study Flow Chart.

10.2.2 Outpatient Administration (Day 4 to Day 28)

From Day 4 to Day 28 daily doses of APL-2 will be administered off-site by a trained nurse or self-administered by the subject, at the subject's home, workplace, or other location convenient to the subject with the exception of Days 8, 15 and 22 (see above).

During the nurse's visit, safety, tolerability and concomitant medication will be monitored.

10.3 Part 2A - Treatment Period – (Days 29 to 84)

Each subject will receive daily SC doses of APL-2 on Days 29 to 84. APL-2 will be administered at the clinical site by study personnel or off-site by the subject themselves or by a study nurse. If a perceived clinical benefit is not observed, treatment will stop on Day 28. The subject will skip Part 2A and enter Part 3 for safety follow up visits.

10.3.1 On Site Administration (Days 29, 36, 43, 57 and 71)

Daily SC doses of APL-2 on Days 29, 36, 43, 57 and 71 will be administered at the clinical site.

Blood samples for laboratory analysis, PK/PD and antigenicity will be taken during site visits as outlined in the Study Flow Chart in Section 3.

Specific procedures for each visit are listed in the Study Flow Chart.

10.3.2 Outpatient Administration (Day 30 to Day 84)

From Day 30 to Day 84 daily doses of APL-2 will be administered off-site by a trained study nurse or self-administered by the subject, with the exception of Days 36, 43, 57 and 71 (see above).

During the nurse's visit, safety, tolerability and concomitant medication will be monitored.

10.4 Part 2B - Treatment Period – (Days 85 to 364)

Each subject will receive daily SC doses of APL-2 on Days 85 to 364. APL-2 will be administered at the site by study personnel or off-site by a study nurse or self-administered by the subject. If a clinical benefit is not observed, treatment will stop on Day 84. The subject will skip Part 2B and enter Part 3 for safety follow up visits.

At the day 85 visit, if required, subjects will receive:

- boosters for Neisseria meningitides types A, C, W, Y and B
- PPSV23 vaccination

On Site Administration (Days 85, 113, 141, 169, 197, 225, 253, 281, 309, and 337)

Daily SC doses of APL-2 on Days 85, 113, 141, 169, 197, 225, 253, 281, 309, and 337 will be administered at the clinical site.

Blood samples for laboratory analysis, PK/PD and antigenicity will be taken during site visits as outlined in the Study Flow Chart in Section 3.

Specific procedures for each visit are listed in the Study Flow Chart.

At the completion of Part 2B, subjects will be offered entry into an open-label extension study (Study APL2-307). Should the subjects not enter the open label extension study, they will exit the study and return to the site for Part 3 Follow-up, as outlined in Section 10.5.

NOTE: Some subjects who complete Part 2B and wish to transition into the open-label extension study may be required to dose beyond the planned conclusion of Part 2B (Day 364) in this study. This study utilizes an acetate buffered mannitol formulation of APL-2. The open-label extension study will utilize an alternate acetate buffered sorbitol formulation. Some subjects may complete Part 2B of this study before there is sufficient availability of the alternate acetate buffered sorbitol formulation to conduct Study APL2-307. Subjects who complete Part 2B prior to Study APL2-307 being open for enrollment to subjects in this study may continue dosing with the acetate buffered mannitol formulation under this protocol until the extension study is open to them for enrollment. These subjects will continue their APL-2 dose and regimen and will return to the site for visits at bi-monthly intervals until the extension study is open to them. Details regarding procedures for dosing beyond Part 2B are provided in Appendix 1 (Section 16). Subjects that transition to either the extension study or Part 2C must complete the Day 365 visit procedures for this study. For these subjects, the Day 365 visit will also be the first visit of the extension study or Part 2C.

10.4.1 Outpatient Administration (Day 85 to Day 364)

From Day 85 to Day 364 daily doses of APL-2 will be administered off-site by a trained study nurse or self-administered by the subject, with the exception of Days when the subject attends clinic visits (see above).

During the nurse's visit, safety, tolerability and concomitant medication will be monitored.

10.5 Part 3 - Follow-up - (Days 365, 379, and 393, or Days 85, 99, and 113, or Days 29, 43, and 57)

All subjects who complete Part 2B, and are not transitioning to the open-label study (or Part 2C), of the study will be asked to return to the clinical facility in Part 3 for follow-up visits on Days 365, 379, and 393. All subjects who complete Part 2A but do not enter Part 2B of the study will be asked to return to the clinical facility in Part 3 for follow-up visits on Days 85, 99 and 113. All subjects who are not eligible to enter Part 2A of the study will be asked to return to the clinical facility in Part 3 for follow-up visits on Days 29, 43 and 57.

Subjects that transition to either the extension study or Part 2C must complete the Day 365 visit procedures for this study, but will not complete the remaining Part 3 visits. For these subjects, the Day 365 visit will also be the first visit of the extension study or Part 2C.

For subjects who skip Part 2A, the boosters for *Neisseria meningitides* vaccines (if needed) should be administered on Day 57 of Part 3.

Specific procedures including blood collection for laboratory analysis, PK/PD and antigenicity for each visit are listed in the Study Flow Chart.

10.5.1 Exit Visit (Day 414, or Day 134, or Day 78)

All subjects will be asked to return to the clinical facility for the Exit Visit 7 weeks after the final dose of APL-2.

Study participation for each subject will be concluded following completion of the Exit Visit. Subjects who complete Part 2B and Part 3 of the study will attend an Exit Visit on Day 414. Subjects who are not eligible to enter Part 2B but complete Part 2A of the study will attend an Exit Visit on Day 134. Subjects who are not eligible to enter Part 2A but complete Part 3 of the study will attend an Exit Visit on Day 78. If a subject withdraws from the study prior to the scheduled Exit Visit, all Exit Visit evaluations should be performed at the subject's final visit to the clinic, including the collection of blood samples for PK and/or PD assessments, as well as a post-dose antigenicity sample if not yet collected.

The Exit Visit procedures are listed in the Study Flow Chart in Section 3.

10.5.2 Unscheduled Follow-up Visits

Note: as part of the dose-escalation decision, 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 facility for additional follow-up visits if considered necessary by the PI 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 3.

10.5.3 Scheduled End of Study

The end of the study is scheduled after completion of the Exit Visit evaluations in the 2 cohorts or after dose-limiting clinical safety endpoints have been reached to preclude further increases of dose. The clinical conduct of the study is intended to last approximately 24 months, including screening.

This time period may change in the event that the study is terminated early, additional cohorts are enrolled, additional time is required to review safety between cohorts, extended safety and PK sampling is added for a cohort (e.g., extended beyond Day 414), or a decision is made to complete an unscheduled analysis between cohorts.

10.6 Dose Escalation and Periodic Safety Review

A decision to proceed to the next dose level (i.e. Cohort 2) will be made by a Safety Review Committee following the review of all pertinent data of Cohort 1. The review will comprise all cumulative safety, tolerability and efficacy data (e.g., physical examinations, ECGs, vital signs, clinical laboratory tests, and adverse events [AEs]) and a thorough assessment of all safety data will occur prior to initiation of Cohort 2. PK/PD data and predicted exposure for subsequent doses based on emerging PK data will also be reviewed prior to determining the proposed dose for Cohort 2. Dose escalation will not occur before all subjects in Cohort 1 have reached the Day 29 visit.

The same review process will be followed if any additional cohorts are added to the study.

10.6.1 Safety Monitoring Committee

A Safety Monitoring Committee (SMC) will review cumulative safety/tolerability data (e.g., physical examinations, ECGs, vital signs, clinical laboratory tests, and adverse events [AEs]), efficacy (LD levels, haptoglobin levels, Hb levels, reticulocyte counts, and RBC transfusions) and PK data including predicted exposures for subsequent doses based on emerging PK data. The SMC will have the responsibility to conduct a thorough safety assessment at regular (monthly) intervals during the treatment phase of the study. A key responsibility of the SMC will be to decide whether to continue or modify the study and to allow dose escalation based on recommendations by the sponsor and upon an evaluation of emerging safety and efficacy data. The SMC will comprise at a minimum of the PIs, a sponsor representative, a PNH expert not involved in the study and an Infectious Disease Specialist. The SMC met approximately every 4 weeks commencing after all subjects in Cohort 1 had reached Day 28. For the remainder of the study, regular or *ad hoc* SMC data reviews will be scheduled approximately every 8 weeks, or as recommended by the SMC or requested by the Sponsor.

If efficacious and safe, APL-2 may reduce LD levels, improve Hb levels and reduce transfusion dependency in these patients. The SMC will be responsible for reviewing individual subject data to understand if there is a health benefit in these individuals at any time during the treatment period. If a benefit is observed the SMC may recommend extending the treatment beyond 364 days either through a protocol amendment or an extension study.

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

10.7 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 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.

11. ASSESSMENTS

11.1 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.

11.1.1 Body Height and Weight

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

11.1.2 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 3.

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.

11.1.3 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 3.

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 the days that APL-2 is administered by a study nurse or other study personnel, 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.

11.1.4 Electrocardiogram Monitoring

Single 12-lead ECGs will be done at the time points outlined in the Study Flow Chart in Section 3.

If done on dosing days, ECGs will be performed within approximately 30 min after dosing. NB ECG on Day 1 must be taken before administration of the 1st dose of Ciprofloxacin.

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.

11.1.5 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 3. 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).

11.1.6 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Study Flow Chart in Section 3. 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:

11.1.6.1 Hematology

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

11.1.6.2 Coagulation

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

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

11.1.6.3 Serum Chemistry

- Blood urea nitrogen (BUN)
- Creatinine
- Bilirubin (total and direct)
- Albumin
- Alkaline phosphatase (ALP)
- Lactate dehydrogenase (LD)
- Haptoglobin
- Gamma-glutamyl transpeptidase (GGT)
- Creatine kinase (CK)
- Aspartate aminotransferase (AST)
- ALT
- Uric acid
- Glucose
- Sodium
- Potassium
- Chloride
- Ferritin
- B12/folate
- Total Iron Binding Capacity (TIBC)

11.1.6.4 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.

11.1.6.5 Serology

- HIV
- HBsAg
- HBV DNA (if required)
- HCV

11.1.6.6 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.

11.1.7 Injection Site Assessment

On the days that APL-2 is administered by a study nurse or other study personnel, an assessment of the APL-2 injection site will be performed within 30 min after 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, induration, and bruising; and the subject will be asked about the presence of pain and/or tenderness. 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.

11.2 Pharmacokinetic Assessments

11.2.1 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 3.

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.

Preliminary PK analysis may be performed to reconsider sampling time points as the study progresses.

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

11.2.2 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.

11.3 Pharmacodynamic Assessments

Blood samples will be collected via direct venipuncture at the time points delineated in the Study Flow Chart in Section 3. for PD assessment of complement activation through the classical (e.g., CH50) and alternative (e.g., AP50) pathways, PNH clone distribution, and C3 deposition on RBCs. 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 Laboratory Reference Manual prior to study initiation.

11.4 Blood Volume for Study Assessments

Table 2: Blood Volume during Study (up to Day 85)

Assay	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Pharmacokinetics	23	2	46
Anti-APL-2 Ab assay	11	2	22
Hematology	24	3	72
Chemistry (Incl. screen serology and pregnancy)	30	3	90
Coagulation profile	24	4.5	108
Complement profile (C3, CH50 and AP50)	24	4	96
Flow cytometry for PNH and C3 deposition	24	2	48
Plasma Hb	24	4	96
		Total Approximate Blood Volume for Study:	**578****

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

** If dose is increased during Part 2B, additional blood draws will be scheduled requiring an additional blood volume of 45 mL.

11.5 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 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 and 90 days after their last dose of study drug.

12. ADVERSE EVENTS

12.1 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.

12.2 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

12.3 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.

12.3.1 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.

12.3.2 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

12.3.3 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.

12.4 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 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 will request clarification of omitted or discrepant information from the initial report. The PI 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 PI must sign and date the form.

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

12.5 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.

12.6 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.

12.7 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.

12.8 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.

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).

13. STATISTICS

13.1 Sample Size Justification

As this is a pilot study the sample size is not based on formal statistical testing. The sample size is considered sufficient to obtain useful safety, tolerability, PD and PK data to assist the planning of future studies.

13.2 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.

13.2.1 Analysis Populations

13.2.1.1 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.

13.2.1.2 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.

13.2.1.3 Pharmacokinetic (PK) Population

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

13.2.1.4 Pharmacodynamic (PD) Population

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

13.2.1.5 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.

13.2.2 Study Endpoints

13.2.2.1 Safety Endpoints

The primary safety endpoints of the study are the number and severity of TEAEs, however 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.

13.2.2.2 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 pre-dose assessment on Day 1.

13.2.2.3 Secondary Endpoints

The FACIT Fatigue Scale (Version 4) is a secondary endpoint. The changes from baseline will be calculated for each post dose assessment, where the baseline will be taken as the pre-dose assessment on Day 1.

The changes from baseline in reticulocyte count and the number of RBC transfusions per month are also included as secondary endpoints.

13.2.2.4 Pharmacokinetic Endpoints

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

13.2.2.5 Exploratory Pharmacodynamic Endpoints (Markers)

Changes from baseline and percentage changes from baseline will be calculated for each of the complement parameters (e.g. CH50, AP50 and C3), C3 deposition on RBC cells and clonal distribution of PNH RBCs. Baseline will be taken as the pre-dose measurement on Day 1.

13.2.3 Safety Analyses

All safety endpoints will be evaluated using the Safety Population.

13.2.3.1 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.

A by-subject TEAE data listing, including verbatim term, preferred term, treatment, severity, and investigator judgment of relationship to treatment, will be provided. The number of subjects reporting each preferred term within each system organ class will be tabulated by cohort. Tabulations will be produced for all TEAEs and for those considered potentially treatment related (causality to study drug is reported as possibly or probably, or where causality is not reported). The number of TEAEs will also be presented; both the total number of TEAEs and the total number counting only unique terms within each subject.

13.2.3.2 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.

13.2.3.3 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 and summarized by study visit.

13.2.4 Efficacy and Secondary Endpoint Analyses

The efficacy endpoints will be evaluated for the ITT Population.

Individual's data will be listed along with changes from baseline and percentage changes from baseline (where appropriate) for each visit. Data will be plotted by study day with each cohort being identifiable.

Absolute values and changes from baseline will be summarized over time.

13.2.5 Pharmacokinetic Analyses

The PK concentrations will be evaluated using the PK Population.

Individual concentration over time profile plots will be presented, with each cohort being identifiable. Median concentration over time profiles will also be plotted. Both linear-linear and linear-log plots will be presented. Concentrations will be summarized over time.

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:

AUC0-t The area under the serum concentration versus time curve, from time 0 to the last measurable concentration (t).

Cmax Maximum observed serum concentration.

These parameters will be summarized.

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).

13.2.6 Pharmacodynamic Analyses

The PD parameters will be evaluated using the PD Population.

Individual parameter over time profile plots will be presented, with each cohort being identifiable. Both changes from baseline and percentage changes from baseline will be presented.

Absolute values and changes from baseline will be summarized over time.

13.2.7 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.

13.2.8 Other Data Analyses

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

13.3 Interim Analyses

As mentioned in Section 9.5, 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 subsequent reports.

14. ADMINISTRATIVE CONSIDERATIONS

14.1 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.

14.2 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.

14.2.1 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.

14.3 Ethics

14.3.1 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).

14.3.2 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.

14.3.3 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 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.

14.3.4 Confidentiality

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

14.3.5 ClinicalTrials.gov

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

14.3.6 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.

14.4 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.

14.5 Protocol Amendments

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

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

14.6 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).

14.7 Finance and Insurance

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

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

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.

15. REFERENCES

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16. APPENDIX 1: PART 2C: MAINTANENCE DOSING PERIOD (IF NECESSARY TO MAINTAIN TREATMENT WITH APL-2 PRIOR TO TRANSITION TO EXTENSION STUDY)

16.1 Overview and Rationale

Subjects who complete Part 2B and have demonstrated clinical benefit from treatment with APL-2 are eligible to transition into a separate open-label extension study in order to continue treatment (Study APL2-307). While Study APL2-CP-PNH-204 utilizes an acetate buffered mannitol formulation of APL-2, the open-label extension study will utilize an alternate acetate buffered sorbitol formulation. Some subjects may complete Part 2B of this study before there is sufficient availability of the alternate acetate buffered sorbitol formulation to allow subjects from this study to transition into Study APL2-307.

As an interim measure, an amendment to the current protocol is required to ensure that subjects are able to continue treatment with APL-2 with the current formulation under Study APL2-CP-PNH-204.

Subjects who complete Part 2B prior to Study APL2-307 being open for enrollment to subjects in this study may continue their APL-2 dose and regimen as Part 2C of the study, until the option becomes available for entry into Study APL2-307. Subjects that participate in Part 2C must complete the Day 365 visit procedures as outlined in the schedule of assessments, with the addition of APL-2 dosing and dispensation. The Day 365 visit that is the first visit of Part 3 will also be the first visit of Part 2C. Beginning at Day 365, these subjects will return to the site for visits at 8-week intervals until the extension study is available. The duration of participation beyond Part 2B will be a different for each subject, depending on the date each subject completes Part 2B. Study objectives will be assessed through Part 2B. Data obtained from subjects who participate in Part 2C will not be included in endpoint assessment and will be only listed.

Once enrollment into the extension study is available for subjects in Study APL2-CP-PNH-204, the conclusion of Part 2B will be the end of the treatment period for this study.

16.2 Part 2C Study Procedures

Subjects will return for the Day 365 study visit and will continue their previous APL-2 dose and regimen. Additional Study Visits will be scheduled at 8-week intervals. Study assessments will be conducted as outlined in the Part 2C Study Flow Chart (Section 16.3).

Each subject will continue to receive daily SC doses of APL-2 from Day 365 until extension study transition or treatment discontinuation. Subjects who discontinue dosing at any time during Part 2C prior to enrollment into the open-label extension Study APL2-307 should conduct the Part 3 safety follow up visits as outlined in Section 10.5.

When enrollment into Study APL2-307 is available to subjects participating in Part 2C, subjects should conduct exit visit procedures as outlined in the Part 2C Study Flow Chart (Section 16.3). The exit visit for Part 2C will be the same day as the subject's first visit for APL2-307.

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

Blood samples for laboratory analysis, PK/PD and antigenicity will be taken during site visits as outlined in the Part 2C Study Flow Chart (Section 16.3).

Specific procedures for each visit are listed in the Part 2C Study Flow Chart (Section 16.3).

16.3 Part 2C Study Flow Chart (Day 365+ as needed)

Study Period	**Part 2C - Treatment (Daily from Day 365 to opening of enrollment to APL2-307)[A]**				
Study Week	53 to 60		61+		Exit Visit **C**
Study Day	365 **B**	366 to 420	421+[A]	56 Day Interval[A]	
Visit Window (+/- Days)			7		
Informed Consent	X				
Preventive antibiotic D	X	X	X	X	
Physical examination E	X		X		
12-lead electrocardiogram F	X		X		
APL-2 administration G	S	H	S	H	
Injection site assessment I	X	X	X	X	
Concomitant medications	X	X	X	X	X
Vital sign measurements J	X	X	X	X	
Urinalysis	X		X		
Blood K	X		X		
Pharmacokinetics **K**	X		X		
Anti-APL-2 Ab assay	X		X		
Hematology and chemistry	X		X		
Coagulation profile **L**	X		X		
Complement profile (C3, CH50 and AP50)	X		X		
Flow cytometry for PNH/C3 deposition	X		X		
Plasma Hb	X		X		
Urine pregnancy test M	X		X		
FACIT fatigue Scale	X		X		
Adverse events N	X	X	X	X	X
Thrombosis record (MAVE)	X	X	X	X	

See study flow chart footnotes on next page

FOOTNOTES:

A. Beginning at Day 365, subjects who need to continue dosing with APL-2 will schedule additional study visits at 8-week intervals until subjects in this study are eligible to enroll into the open-label extension Study APL2-307. Subjects who discontinue dosing at any time during Part 2C prior to enrollment into the open-label extension Study APL2-307 should conduct the Part 3 safety follow up visits.

B. The Day 365 visit that is the first visit of Part 3 will also be the first visit for Part 2C. Procedures will not be duplicated.

C. When enrollment into APL2-307 is available to subjects participating in Part 2C, subjects should return to the site to conduct exit visit procedures. The Part 2C exit visit will be the same day as the first visit for Study APL2-307.

D. Penicillin V 500 mg twice daily.

E. 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.

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

G. 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 continued clinical benefit.

H. Reserved – See note E.

I. Injection site assessment will be performed within 30 minutes after APL-2 administration. Ambulatory syringe infusion pump training will include instructions to report any injection site reaction to the PI.

J. If APL-2 is administered by a study nurse or other research study staff, vital signs will be measured within 2 hours prior to dosing and within 30 minutes after dosing. If APL-2 is self-administered, pre- and post-dose vital signs will not be measured.

K. Blood samples will be taken pre-dose

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

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

N. Ambulatory syringe infusion pump training will include instructions to report any adverse events to the PI.