Statistical Analysis Plan

Sponsor Name:	Apellis Pharmaceuticals, Inc.
Protocol Number:	APL2-CP-PNH-204
Protocol Title:	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:	1.0 (16th September 2015)
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Author(s):	PPD
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SAP Version Date:	19th December 2019

Signature Page

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I confirm that I have reviewed this document and agree with the content.

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Apellis Pharmaceuticals, Inc.

TABLE OF CONTENTS

1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ATC	Anatomic Therapeutic Chemical
AUC	Area Under the Curve
BLQ	Below Limit of Quantification
CNS	Clinical Network Services Pty Ltd
CSR	Clinical Study Report
ECG	Electrocardiograms
FACIT	Functional Assessment of Chronic Illness Therapy
ITT	Intent To Treat
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
QTcB	Heart Rate Corrected QT interval, using Bazett's formula
QTcF	Heart Rate Corrected QT interval, using Fridericia's formula
PD	Pharmacodynamics
PNH	Paroxysmal Nocturnal Hemoglobinuria
PK	Pharmacokinetics
PRBCs	Packed Red Blood Cells
PP	Per Protocol
PT	Preferred Term
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error

Abbreviation	Description
SMC	Safety Monitoring Committee
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures, Listings
ULN	Upper Limit of Normal
WHO	World Health Organization

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives. Any amendments to the SAP will be made prior to database lock. Any additional analyses not described in the final SAP or deviations from the final SAP will be documented in the clinical study report (CSR).

2.1. RESPONSIBILITIES

Clinical Network Services Pty Ltd (CNS) will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings (TFLs). Pharmacokinetic (PK) parameters will be derived by JPharma Solutions.

3. STUDY OVERVIEW

3.1. STUDY OBJECTIVES

The objectives of the study are to assess safety, tolerability, preliminary efficacy and pharmacokinetics (PK) of multiple subcutaneous (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 subjects.

3.2. STUDY DESIGN

This section details the study design as documented in Protocol Amendment 8. Additional details of all protocol amendments are detailed in Appendix 1.

This is a Phase 1b, open label, multiple ascending dose pilot study in subjects with PNH who have not received eculizumab (Soliris®) in the past. The study is planned to enrol approximately 23 subjects across 2 cohorts. Cohort 1 has enrolled 3 subjects who were dosed with 180 mg/day APL-2 subcutaneously for 28 days. Cohort 2 will include up to 20 subjects that 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 PI and the sponsor, in consultation with the Safety Monitoring Committee (SMC), to repeat a dose level or to study an intermediate dose level.

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 PD and APL-2 PK.

The study will consist of the following parts:

1. Part 1 – subjects will receive APL-2 for 28 days
2. Part 2A – subjects may continue to receive APL-2 for a further 56 days (i.e. until Day 84) if there is evidence of perceived clinical benefit following review of available safety, PK and PD data by the investigator and sponsor
3. Part 2B - subjects may continue to receive APL-2 for a further 280 days (i.e. until Day 364) if there is ongoing evidence of perceived clinical benefit following review of available safety, PK and PD data by the investigator and sponsor
4. Part 2C – continuation of APL-2 treatment if enrolment into the extension study (APL2-307) is not open. This part was also introduced as part of a country specific amendment in New Zealand to allow an ongoing subject to continue to receive APL-2 treatment for up to 2 years.
5. Part 3 – safety follow up (if applicable; subjects may transition into an open label extension study to continue treatment with APL-2 after the completion of Part 2B)

Cohort 2 was not initiated until all subjects in Cohort 1 had reached the Day 29 visit and the SMC had reviewed emerging safety and efficacy data and determined that, at the initial dose, APL-2 has an acceptable safety and tolerability profile. No subjects in Cohort 1 progressed to Part 2A.

If a Cohort 2 subject has a sub-optimal clinical response during daily dosing with 270 mg APL-2 in Part 2B, the dose may be increased up to 360 mg/day. Doses will be administered at the clinical site every 2 weeks for the first 6 weeks after commencing the higher dose.

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

During Part 1, the first 3 daily SC doses of APL-2 (Days 1 to 3) as well as doses on Days 8, 15 and 22 will be administered at the clinical site. All other daily doses of APL-2 from Days 4 to 28 will be administered by a nurse or self-administered by the subject, at the subject's home, workplace, or other location convenient to the subject. Cohort 2 subjects progressing to Part 2A of the study will continue to receive daily doses of APL-2 until Day 84. Cohort 2 subjects progressing to Part 2B of the study will continue to receive daily doses of APL-2 until Day 364. Doses will be administered by a 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.

Subjects who complete Part 2B will be eligible to transition into an open-label extension study in order to continue to receive treatment with APL-2. Subjects who elect to transition into the extension study will not complete Part 3 of this study. Some subjects that complete Part 2B and wish to transition into the extension study may be required to dose beyond the planned conclusion of Part 2B (Day 364) in this study until the extension study is open for enrolment. These subjects will continue with their current APL-2 dose and regimen and enter Part 2C of the study. During Part 2C they will return to the site for visits at bi-monthly intervals (refer to Protocol Amendment 8

Appendix 1 for details of dosing and visit schedule and procedures). 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.

For subjects who do not enter Part 2A treatment will be stopped on Day 28 and the subject will enter Part 3 for safety follow-up visits on Days 29, 43, 57 and 78 (exit visit). For subjects who do not enter Part 2B treatment will be stopped on Day 84 and the subject will enter Part 3 for safety follow-up visits on Days 85, 99, 113 and 134 (exit visit). For subjects who do not enter Part 2C or the open-label extension study, treatment will be stopped on Day 364 and the subject will enter Part 3 for safety follow-up visits on Days 365, 379, 393 and 414 (exit visit).

Study objectives will be based on all data collected throughout the study however the main focus of the study for Cohort 2 is the period up to and including Day 365.

3.3. DETERMINATION OF SAMPLE SIZE

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, PK and PD data to assist the planning of future clinical studies in patients with PNH.

3.4. TREATMENT ASSIGNMENT AND BLINDING

Each subject will be assigned a unique identification number upon entering screening. Subjects who enter both cohorts will be assigned a unique number for each cohort, and a record will be kept to identify unique numbers for the same subject. Subjects who complete the study screening assessments and meet all eligibility criteria will be scheduled to enter the study and dosed in the next available cohort.

The study is open label so blinding is not applicable.

3.5. ADMINISTRATION OF STUDY MEDICATION

Sterile solutions of APL-2 at 150mg/mL in 5% dextrose or in acetate-buffered mannitol (introduced with Amendment 4) or in acetate-buffered sorbitol (introduced with Amendment 5) will be administered subcutaneously. The volume of the injection will be adjusted to achieve the desired dose. 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. Following Amendment 4, subjects may self-administer the SC infusions using an ambulatory syringe pump after receiving appropriate training by research nurses 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.

The planned dose for Cohort 1 was APL-2 180 mg/day and for Cohort 2 is APL-2 270 mg/day (up to

360 mg/day). The dose of 270 mg/day for Cohort 2 was determined by the SMC based on cumulative safety, PK and PD data from Cohort 1. However, subjects with a sub-optimal clinical response in Cohort 2 may have their dose increased to 360 mg/day. The dose will not exceed 360 mg/day for any individual.

3.6. STUDY FLOWCHART

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 Protocol Amendment 8 Appendix 1.

4. ENDPOINTS

4.1. SAFETY ENDPOINTS

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

4.2. EFFICACY ENDPOINTS

The primary efficacy endpoints are changes from baseline and percentage changes from baseline in lactase dehydrogenase (LDH), haptoglobin and hemoglobin. Changes will be calculated for each post dose assessment. Baseline will be the last measurement prior to start of dosing.

4.3. SECONDARY ENDPOINTS

The secondary endpoints include changes from baseline in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale (version 4), change from baseline and percentage change from baseline in reticulocyte count, change from baseline and percentage change from baseline in total bilirubin.

The change from baseline in FACIT fatigue scale, reticulocyte count and total bilirubin will be calculated for each post dose assessment

The baseline RBC transfusions per year will be calculated for the 12 month period prior to screening and prior to Day 1 as the number of transfusions reported in the previous 365 days from screening and from Day 1 respectively. A similar calculation will be used for the baseline number of units transfused per year relative to screening and relative to Day 1. Only whole blood and packed RBC (PRBCs) transfusions will be included in the calculations. For subjects who enter both cohorts the baseline for both cohorts will be taken from the 12 month transfusion history prior to Cohort 1.

4.4. PHARMACOKINETIC ENDPOINTS

Serum APL-2 concentrations will be determined from multiple samples taken during the study.

PK parameters for APL-2 will be estimated from the individual serum concentration-time data over the whole time period (Days 1 to 414) using a non-compartmental approach. PK parameters will include:

- AUC_{total} The area under the serum concentration versus time curve, from time 0 (pre-dose on Day 1) to the last measurable concentration at the end of the study.
- AUC_{365} The area under the serum concentration versus time curve, from time 0

(pre-dose on Day 1) to the concentration recorded on Day 365.

- $C_{trough,max,total}$ Maximum observed pre-dose serum concentration during the study.
- $C_{trough,max,365}$ Maximum observed pre-dose serum concentration up to Day 365.

PK parameters will be calculated using PKNCA (version 0.8.4 or higher) with R (version 3.4.3 or higher).

A separate analysis will combine the PK data with prior data collected in earlier clinical studies to update the APL-2 population PK model. This analysis will be conducted separate to the reporting of this study and will be detailed in a separate population PK SAP.

4.5. PHARMACODYNAMIC ENDPOINTS

The PD endpoints include changes from baseline and percentage changes from baseline for the C3 complement parameter, and changes from baseline and percentage of baseline value for CH50 and AP50.

To reduce variability for the complement parameter AP50, all of a particular subject's samples will be analysed on the same plate. This means that only a subset of samples collected will be analysed for AP50. The subset of samples includes the Screening, Days 1, 29, 85, 169 and 365 samples. Only if there are spurious results will other samples be analysed.

Changes from baseline and percentage changes from baseline will also be derived for C3 deposition on RBC cells (percent C3d CD59 Type I, II and III), clonal distribution of PNH RBCs (percent CD59 Type I, II and III), PNH granulocytes (percent FLAER) and PNH monocytes (percent FLAER).

In addition the following endpoints will be derived:

- Clonal distribution of PNH RBCs (percent Type II + III); this is simply the sum of the clonal distribution of PNH RBCs Type II and Type III.
- C3d deposition on RBC cells (percent Type II + III); this is the number of events for C3d deposition on RBC cells (Type II) plus number of events for C3d deposition on RBC cells (Type III) divided by number of events for PNH CD59 Type II and III expressed as a percent.

4.6. IMMUNOGENICITY DATA

Only a subset of samples collected will be analysed. The subset includes samples collected on Days 1, 29 and 365. For any sample confirmed positive, the remaining samples for that particular subject will be analysed.

Following the Food and Drug Administration's recommendation, any subject that tests positive for anti-drug antibodies will continue to be monitored until values have returned to baseline levels. If necessary, this will include collecting a sample from the subject every 6 months after the

completion of the study. Any samples collected after study completion will be reported separately.

5. ANALYSIS SETS

5.1. SCREENED SET

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

5.2. SAFETY SET / INTENT TO TREAT SET

The safety set will include all subjects eligible to receive study medication and who receive at least one dose of study medication. The intent to treat (ITT) set will be identical to the safety set for this study. All baseline characteristics, demography and efficacy endpoint data will be presented using the ITT set.

5.3. PHARMACOKINETIC SET

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

5.4. PHARMACODYNAMIC SET

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

5.5. PER PROTOCOL SET

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

5.6. PROTOCOL DEVIATIONS

All protocol deviations will be reviewed and documented before database lock. Protocol deviations will be recorded by the site staff, study monitors and medical monitor reviewers. They may also be identified through programmable checks of the data.

Protocol deviations will be categorized by Apellis Pharmaceuticals, Inc. as either major (for example violation of inclusion or exclusion criteria) or minor prior to database lock. All protocol deviations will be listed. No subjects will be excluded from the screened, safety or ITT sets due to protocol

deviations.

5.7. DATA REVIEW FOR ANALYSIS SETS

After all the data has been entered and verified into the database, a review will be performed. The purpose of this review will be to define the analysis sets. The review will also check the quality of the data, identify outliers and make 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.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

No formal statistical testing will be performed on Cohort 1 data. Comparisons to baseline will be performed for Cohort 2.

Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. However, with so few subjects in Cohort 1, continuous data, unless specifically stated otherwise, will only be summarized for Cohort 2.

Categorical variables will be summarized using frequencies and percentages.

Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more decimal place than the original values, and standard deviations should be printed out to 2 more decimal places than the original values. The minimum and maximum should report the same number of decimal places as the original values. Percentages will be displayed with 1 decimal place; except percentages will not be presented when the count is zero and 100% will be presented as an integer.

Unless stated otherwise, baseline will be taken as the pre-dose assessment on Day 1; if this is missing then the screening value or, if available, a pre-dose unscheduled measurement will be used (whichever is closer to the baseline date). For subjects who enter both cohorts the baseline for Cohort 2 will be taken as the pre-dose assessment associated with Cohort 2.

In by-visit summary tables, the baseline will be summarized using all available data, but also for each visit using only the baseline data from subjects with available data at the visit; hence the mean change from baseline will equal the (mean visit value – mean baseline value).

For summary tables that include both cohorts, data will be presented by cohort and overall, unless stated otherwise. The overall summary will be based on unique subjects, so subjects who enter both cohorts will only be counted once.

Where specified, summary tables will be presented by study part (1, 2A, 2B, 2C or 3). For assessments performed at visits e.g. vital signs, this will be based on the study part the visit is assigned to according to protocol. The only exception is the first visit of each part which will be assigned to the previous part as assessments are performed prior to administration of study drug. So Day 29, Day 85 and Day 365 will be assigned to Part 1, 2A and 2B respectively. For event based data e.g. adverse events, the part is assigned based on the event start day (refer to Section 11.2 for more details).

All data will be listed. Data listings will be presented by cohort. Subjects who enter both cohorts will be identified in a footnote on the listings. Data listings will present study days in addition to dates, where study day is derived as (assessment date – first day of dosing+1). The first day of dosing will be identified as Study Day 1. For subjects who enter both cohorts the study day for Cohort 2 will be relative to the first day of dosing in Cohort 2.

For Cohort 2 subjects the last dose received prior to the assessment will also be listed. This will be the dose received prior to the assessment on the same day or the previous day. If a subject does not receive study drug during this time then 'not dosed' will be listed.

All statistical analyses will be performed using SAS® (Version 9.4 or higher, SAS Institute Inc., Cary, NC, USA).

6.2. MISSING DATA

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

Where specified screen values or pre-dose unscheduled measurements may be used as a baseline value in the event of missing Day 1 measurements.

Handling of missing dates/times for the start/stop of medications and adverse events are detailed in Sections 7.4 and 11.2 respectively.

The original data will always be presented in the listings.

6.2.1. Pharmacokinetic and Pharmacodynamic Data

APL-2 concentrations reported as below the limit of quantification (BLQ) will be taken as zero for linear plots, and equal to the lower limit of quantification (LLOQ) for semi-logarithmic plots.

If a BLQ value falls between two quantifiable concentrations the value will be set equal to the LLOQ, unless it's exclusion can be justified (e.g. implausibility given the profile observed and known PK properties).

If a baseline PD value is zero, then the percentage change from baseline will not be calculated. If a

PD value is BLQ then the value will be set to the LLOQ. Similarly, for the PD plots, a BLQ value will be set equal to LLOQ.

6.3. VISIT WINDOWS

Data will be assigned to visits using windowing (see table below). If more than one assessment (including the early termination or unscheduled assessments) falls within the same defined window, the assessment closest to the target day with non-missing data will be considered for analysis. If two assessment dates are at the same distance from the target day, the first assessment with non-missing data will be considered for analysis.

Part	Visit	Target Day	Analysis Window	Interval
1	Baseline	1	≤1*	NA
	Day 8	8	5 – 11	7
	Day 15	15	12 - 18	7
	Day 22	22	19 – 25	7
2A	Day 29	29	26 – 32	7
	Day 36	36	33 – 39	7
	Day 43	43	40 - 46	7
	Day 57	57	54 - 60	7
	Day 71	71	68 - 74	7
2B	Day 85	85	78 - 92	15
	Day 113	113	–106 - 120	15
	Day 141	141	134 - 148	15
	Day 169	169	162 - 176	15
	Day 197	197	190 - 203	15
	Day 225	225	218 - 232	15
	Day 253	253	246 - 260	15
	Day 281	281	274 - 288	15
	Day 309	309	302 - 316	15
	Day 337	337	330 - 344	15
3^	Day 365$	365	358 - 372	15
	Day 379	379	374 – 384	11
	Day 393	393	388 – 398	11
	Day 414	414	409 - 419	11
2C@	Day 421	421	410 - 432	23
	Repeat for visits every 56 days	*Previous target day +56*	*(target day-11) – (target day+11)*	*23*

* Must be prior to dosing if time of assessment is recorded.
^ Days only applicable for those subjects that complete Part 2B of the study and enter Part 3.

[$] All subjects that complete Part 2B will have a Day 365 visit irrespective of whether they enter Part 2C or enter the extension study APL2-307.
[@]Only applicable for subjects entering Part 2C while waiting to enrol in the extension study.

A subject will only be allocated to Part 2A, 2B or 2C visits if they have agreed to enter these phases. Follow-up visits (Part 3), with the exception of Day 365, by design are after the last dose of study drug and should not be allocated to on-treatment visits. Day 365 will be performed for all subjects who complete Part 2B of the study irrespective of whether they are continuing APL-2 treatment. If a subject discontinues from the study early then they will enter the follow up Part 3 phase and the day will therefore not match the days above. In these cases the day will be according to the day post the last study dose but will be allocated to Part 3.

Summary tables by visit will be based on the analysis visit. Data collected outside these windows will only be listed. All listings will include the original visit assignment as well as the analysis visit if it differs from the original visit.

These visit windows will be reviewed and may be updated prior to reporting. Any assessments that fall outside of these windows will be reviewed on a case-by-case basis, and decisions on their handling will be fully documented prior to reporting.

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. PATIENT DISPOSITION AND WITHDRAWALS

The number of subjects screened and the number of subjects entering both cohorts will be presented overall. The following will be presented by cohort:

- Number of subjects starting Part 1
- Number of subjects completed Part 1
- Number of subjects withdrawn during Part 1 and reason for withdrawal
- Number of subjects starting Part 2A
- Number of subjects completed Part 2A
- Number of subjects withdrawn during Part 2A and reason for withdrawal
- Number of subjects starting Part 2B (*Cohort 2 only*)
- Number of subjects completed Part 2B (*Cohort 2 only*)
- Number of subjects withdrawn during Part 2B and reason for withdrawal (*Cohort 2 only*)
- Number of subjects starting Part 2C (*Cohort 2 only*)
- Number of subjects withdrawn during Part 2C and reason for withdrawal (*Cohort 2 only*)
- Number of subjects completed Part 2C (*Cohort 2 only*)
- Number of subjects entering extension study APL2-307 (*Cohort 2 only*)
- Number of subjects completed Part 3 safety follow-up

- Number of subjects withdrawn during Part 3
- Number of subjects in each analysis set

Disposition data will be listed. A visit listing will also be presented which will include all visits (scheduled and unscheduled) along with dates and study days attended and the mapped analysis visit if different from the scheduled visit.

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demography (gender, race, ethnicity, age [years], weight [kg], height [cm] and BMI [kg/m^2]) will be summarized by cohort and overall for the ITT set. Age, weight, height and BMI will be summarized using summary statistics for continuous variables. Gender, race and ethnicity will be summarized using summary statistics for categorical variables.

Time since diagnosis of PNH (years) and the baseline measurements for complement parameters (CH50, AP50 and C3), clonal distribution of PNH RBCs, hemoglobin, LDH, haptoglobin, reticulocyte, total bilirubin and total FACIT score will be summarized by cohort and overall using summary statistics for continuous variable. In addition, the number of transfusions in the 12 months prior to screening and in the 12 months prior to Day 1 will be summarized using summary statistics for continuous variables.

Age = (informed consent date - date of birth + 1)/365.25 truncated to complete years.

Years with PNH = (informed consent date - date of diagnosis + 1)/365.25.

Subjects who enter both cohorts will only be counted once in the overall summary for demographic and baseline characteristics and only data prior to the first cohort will be used in the overall summary. The summaries by cohort will use baseline data from each of the cohorts.

7.3. MEDICAL HISTORY AND CONCOMITANT DISEASES

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0. Summaries will be presented for the ITT set by System Organ Class (SOC) and Preferred Term (PT) with counts for each cohort and overall. Each subject will be counted only once in each SOC or SOC/PT summary.

The number of subjects experiencing past thrombosis and the number of events will be summarized separately by cohort and overall.

Subjects who enter both cohorts will only be counted once in the overall summary for medical history and thrombosis history and only data prior to the first cohort will be used in the overall summary. The summary by cohort will use baseline data from each of the cohorts.

7.4. PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be coded using WHO Drug Dictionary version 2018:03. Medication will be presented for the safety set by Anatomic Therapeutic Chemical (ATC) level 2 (therapeutic main group) and ATC level 5 (standardized medication name) with counts for each cohort and overall. A subject who took more than one medication will be counted only once if these medications belong to the same extended ATC classification.

For the prior medications summary, subjects who enter both cohorts will only be counted once in the overall summary and only data prior to the first cohort will be used in the overall summary. The summary by cohort will use baseline data from each of the cohorts.

For the concomitant medications summary, subjects who enter both cohorts will only be counted once in the overall summary, all concomitant medications from both cohorts will be included in the overall summary.

Prior medications will be defined as those medications started prior to the administration of APL-2 on Day 1. For subjects who enter both cohorts, prior medications for Cohort 2 will only consider those medications recorded on the eCRF for Cohort 2. Concomitant medications will be defined as those medications taken following the first administration of APL-2 on Day 1. Hence medications started before study dosing, but continuing after are considered as both prior and concomitant medications. The listing of medications will identify prior and concomitant medications.

If either the start or stop date of medication is missing, the worst or most conservative case will be considered when assigning medications to categories. So for a missing start date (where stop date is after date of first dose) the date will be imputed as the date of first dose; for a missing stop date the date will be imputed as the date of last dose or start date if start date is after last dose. If a partial date is recorded, the following convention will be used to assign the medication:

- If a partial date is missing a start day and the month/year is the same as first dose date then use first dose date, else '01' will be used for the day; if a start date is missing a month and the year is the same as first dose date then use first dose date, else January will be used for the start month.
- If a partial date is missing a stop day and month/year is same as last study date then use last study date, else last day of the given month will be used for the stop day; if a stop date is missing a month and the year is the same as last study date then use last study date, else December will be used for the stop month.

8. EFFICACY

8.1. EFFICACY ENDPOINTS AND ANALYSIS

8.1.1. Lactate Dehydrogenase, Haptoglobin and Hemoglobin

For each parameter, absolute values will be listed together with changes from baseline and percentage changes from baseline for the ITT set by cohort, part of the study and study visit. Values that are outside the reference range will be flagged. For LDH the value related to their ULN will also be listed and for hemoglobin and haptoglobin the value related to their LLN will be listed.

For Cohort 2, absolute values, changes from baseline and percentage changes from baseline will be summarised, using descriptive statistics, by part of the study and study visit. The associated 95% confidence interval and 2-sided p-value (Student's t-test) for the changes from baseline will also be presented; 95% confidence intervals for the absolute values will also be presented. The number and percentage of subjects ≤ ULN and ≤ 1.5*ULN for LDH will also be summarized by part of the study and study visit (Cohort 2 only). The number and percentage of subjects ≥ LLN for haptoglobin and hemoglobin will also be summarized by part of the study and study visit (Cohort 2 only). The summary will be generated for the ITT and PP analysis sets.

For Cohort 2, mean absolute values with 95% confidence intervals will be plotted by study visit for each parameter. The number of subjects contributing to each mean value at a visit will be presented above the x-axis and a reference line at Day 365 will be included. The LDH and haptoglobin plots will shade the area between the lower and upper limits of normal. As the normal range for hemoglobin is dependent on gender the hemoglobin plot will be repeated for males and females separately and these plots will shade the area between the lower and upper limits of normal for the corresponding gender. If the normal range changes during the study then the widest range across the study will be presented on these plots. The plots will be generated for the ITT and PP analysis sets.

Absolute values, changes from baseline and percentage changes from baseline will be plotted by study day with each subject and cohort being identifiable. Subjects who enter both cohorts will be identified in a footnote. A separate plot will be presented for Part 1 and overall i.e. Part 1, 2A, 2B, 2C and 3 combined. A dotted line will be used to identify follow-up (Part 3). The actual sampling day will be used on the x-axis. The absolute value plots will include a reference line at Day 1 and the change and percentage change from baseline plots will include a reference line for 0 on the y-axis. A reference line at Day 365 will also be added for the plot covering the whole study.

Values of LDH, reticulocytes and total bilirubin related to their ULN (i.e. value/ULN) throughout the study will be plotted against time for each subject in Cohort 2 individually (i.e. one plot per subject). Hemoglobin and haptoglobin values will also be included but related to their LLN (i.e. value/LLN). Each parameter will have a different symbol and a legend will identify the parameters included. A reference line of 1 on the y-axis will be included. On study transfusions (PRBC only) will be identified

on the plot as a vertical line at the relevant study day. Above the profile plot a separate plot will be displayed which shows the APL-2 dose by study day. The study day on both plots will be aligned.

8.2. SECONDARY ENDPOINTS AND ANALYSIS

8.2.1. FACIT Fatigue Scale

Absolute FACIT fatigue scores will be listed together with change from baseline for the ITT set by cohort, part of study and study visit.

For Cohort 2, absolute values and changes from baseline will be summarised, using descriptive statistics, by part of the study and study visit. The associated 95% confidence interval and 2-sided p-value (Student's t-test) for the changes from baseline will also be presented; 95% confidence intervals for the absolute values will also be presented. The summary will be generated for the ITT and PP analysis sets.

For Cohort 2, mean absolute values with 95% confidence intervals will be plotted by study visit. The number of subjects contributing to each mean value at a visit will be presented above the x-axis and a reference line at Day 365 will be included. The plot will be generated for the ITT and PP analysis sets.

Absolute values and changes from baseline will be plotted by study day with each subject and cohort being identifiable. Subjects who enter both cohorts will be identified in a footnote. A separate plot will be presented for Part 1 and overall i.e. Part 1, 2A, 2B, 2C and 3 combined. A dotted line will be used to identify follow-up (Part 3). The actual sampling day will be used on the x-axis. The absolute value plots will include a reference line at Day 1 and the change from baseline plots will include a reference line for 0 on the y-axis. A reference line at Day 365 will also be added for the plot covering the whole study.

Values of FACIT fatigue scores throughout the study will be plotted against time for each subject in Cohort 2 individually (i.e. one plot per subject). On study transfusions (PRBC only) will be identified on the plot as a vertical line at the relevant study day. Above the profile plot a separate plot will be displayed which shows the APL-2 dose by study day. The study day on both plots will be aligned.

8.2.2. Reticulocyte and Total Bilirubin

For each parameter, absolute values will be listed together with change from baseline and percentage change from baseline for the ITT set by cohort, part of study and study visit. Values that are outside the reference range will be flagged and value related to their ULN will be listed.

For Cohort 2, absolute values, changes from baseline and percentage changes from baseline will be summarised, using descriptive statistics, by part of the study and study visit. The associated 95% confidence interval and 2-sided p-value (Student's t-test) for the changes from baseline will also be

presented; 95% confidence intervals for the absolute values will also be presented. The number and percentage of subjects ≤ ULN and ≤ 1.5*ULN will also be summarized by study visit for Cohort 2 only. The summary will be generated for the ITT and PP analysis sets.

For Cohort 2, mean absolute values with 95% confidence intervals will be plotted by study visit for each parameter. The number of subjects contributing to each mean value at a visit will be presented above the x-axis and a reference line at Day 365 will be included. The reticulocyte plot will shade the area between the lower and upper limits of normal. As the normal range for total bilirubin is dependent on gender the total bilirubin plot will be repeated for males and females separately and these plots will shade the area between the lower and upper limits of normal for the corresponding gender. If the normal range changes during the study then the widest range across the study will be presented on these plots. The plots will be generated for the ITT and PP analysis sets.

Absolute values, changes from baseline and percentage changes from baseline will be plotted by study day with each subject and cohort being identifiable. Subjects who enter both cohorts will be identified in a footnote. A separate plot will be presented for Part 1 and overall i.e. Part 1, 2A, 2B, 2C and 3 combined. A dotted line will be used to identify follow-up (Part 3). The actual sampling day will be used on the x-axis. The absolute value plots will include a reference line at Day 1 and the change and percentage change from baseline plots will include a reference line for 0 on the y-axis. A reference line at Day 365 will also be added for the plot covering the whole study.

8.2.3. RBC Transfusions

All 12 month transfusion history data and on study transfusion data will be listed by Cohort. A separate listing of the baseline number of transfusions per year and baseline number of units transfused per year relative to screening and relative to Day 1 will also be included.

9. PHARMACOKINETICS

9.1. CONCENTRATION DATA

The APL-2 concentrations will be evaluated using the PK set. For Cohort 2, APL-2 concentrations will be summarized by study visit and dose level (270 mg or 360 mg) using descriptive statistics (and standard error [SE) will also be presented). The number of subjects with a BLQ value will also be tabulated.

Linear and log-linear individual concentration profile plots against time will be produced with each subject and cohort being identifiable. Subjects who enter both cohorts will be identified in a footnote. A separate plot will be presented for Part 1 and overall i.e. Part 1, 2A, 2B, 2C and 3 combined. A dotted line will be used to identify follow-up (Part 3). The actual sampling day will be used on the x-axis.

Linear and log-linear mean (± SE) concentration plots against study visit will be generated. The

number of subjects contributing to each mean value at a visit will be presented above the x-axis and a reference line at Day 365 will be included.

A listing of all concentration data will be presented by cohort. The actual time and deviation from nominal time will also be listed.

9.2. PHARAMCOKINETIC DATA

APL-2 PK parameters, $AUC_{total,}$ AUC_{365} $C_{trough,max,total}$ and $C_{trough,max,365}$, will be estimated from the individual serum concentration time data, using a non-compartmental approach. For Cohort 2, $C_{trough,max}$ and $C_{trough,max,365}$ will be calculated for both 270mg and 360mg where subjects receive both doses. AUC_{total} and AUC_{365} will be calculated using the linear-log trapezoidal method. BLQ values in the elimination phase will be considered missing.

PK parameters will be listed by cohort. Additionally, for Cohort 2, PK parameters will be summarized using descriptive statistics. Geometric mean and CV will also be presented.

10. PHARMACODYNAMICS

The PD parameters, complement parameters (CH50, AP50 and C3), C3 deposition on RBC cells (percent C3d CD59 Type I, II, III and II+III) clonal distribution of PNH RBCs (percent CD59 Type I, II, III and II+III), PNH granulocytes (percent FLAER) and PNH monocytes (percent FLAER), will be evaluated using the PD set.

Absolute PD parameter values will be listed together with changes from baseline and percentage changes from baseline (for CH50 and AP50 percentage of baseline will be listed instead), by cohort, part of the study and study visit.

For Cohort 2, complement parameter C3, absolute values, changes from baseline and percentage changes from baseline will be summarised, using descriptive statistics, by part of the study and study visit. The associated 95% confidence interval and 2-sided p-value (Student's t-test) for the changes from baseline will also be presented. A similar summary will also be produced for the complement parameters CH50 and AP50 however percentage of baseline values will be summarized instead of percentage changes from baseline. For AP50 only study visits baseline, Days 29, 85, 169 and 365 will be summarized.

For Cohort 2, mean absolute values with 95% confidence intervals will be plotted by study visit for the complement parameters (C3, CH50 and AP50). The number of subjects contributing to each mean value at a visit will be presented above the x-axis and a reference line at Day 365 will be included.

For Cohort 2, C3 deposition on RBC cells (percent C3d CD59 Type I, II, III and II+III), clonal distribution of PNH RBCs (percent CD59 Type I, II, III and II+III), PNH granulocytes (percent FLAER) and PNH

monocytes (percent FLAER), absolute values and changes from baseline will be summarised, using descriptive statistics, by study visit.

For Cohort 2, mean absolute values with 95% confidence intervals will be plotted by study visit for C3 deposition on RBC cells (percent C3d CD59 Type II+III) and clonal distribution of PNH RBCs (percent CD59 Type II+III). The number of subjects contributing to each mean value at a visit will be presented above the x-axis and a reference line at Day 365 will be included.

Absolute values, changes from baseline and percentage changes from baseline will be plotted for the complement parameter C3 by study day with each subject and cohort being identifiable. Subjects who enter both cohorts will be identified in a footnote. A separate plot will be presented for Part 1 and overall i.e. Part 1, 2A, 2B, 2C and 3 combined. A dotted line will be used to identify follow-up (Part 3). The actual sampling day will be used on the x-axis. The absolute value plots will include a reference line at Day 1 and the change and percentage change from baseline plots will include a reference line for 0 on the y-axis. A reference line at Day 365 will also be added for the plot covering the whole study.

For the complement parameters CH50 and AP50 only percentage of baseline values will be plotted by study day with each subject and cohort being identifiable. Subjects who enter both cohorts will be identified in a footnote. A separate plot will be presented for Part 1 and overall i.e. Part 1, 2A, 2B, 2C and 3 combined. A dotted line will be used to identify follow-up (Part 3). The actual sampling day will be used on the x-axis. A reference line for 100 will be presented on the y-axis and a reference line at Day 365 will also be added for the plot covering the whole study.

For the complement parameter C3 values throughout the study will be plotted against time for each subject in Cohort 2 individually (i.e. one plot per subject). On study transfusions (PRBC only) will be identified on the plot as a vertical line at the relevant study day. Above the profile plot a separate plot will be displayed which shows the APL-2 dose by study day. The study day on both plots will be aligned. For the complement parameters CH50 and AP50 the same plot will be generated using percentage of baseline values instead.

Absolute values in PNH granulocytes (percent FLAER) will be plotted by study day with each subject and cohort being identifiable. Subjects who enter both cohorts will be identified in a footnote. A separate plot will be presented for Part 1 and overall i.e. Part 1, 2A, 2B, 2C and 3 combined. A dotted line will be used to identify follow-up (Part 3). The actual sampling day will be used on the x-axis. The absolute value plot will include a reference line at Day 1. A reference line at Day 365 will also be added for the plots covering the whole study. These plots will be repeated for PNH monocytes (percent FLAER).

Individual subject plots of the percentage distribution will be presented for the C3 deposition on RBC cells parameters, with all parameters included on the same subject plot, for Part 1 and overall i.e. Part 1, 2A, 2B, 2C and 3 combined. A dotted line will be used to identify follow-up (Part 3). The actual sampling day will be used on the x-axis. The plots will include a reference line at Day 1. The

overall plots (i.e. Part 1, 2A, 2B, 2C and 3 combined) will identify on study transfusions (PRBC only) as a vertical line at the relevant study day; and above the profile plot a separate plot will be displayed which shows the APL-2 dose by study day. The study day on both plots will be aligned. These plots will be repeated for clonal distribution of PNH RBCs parameters.

Clonal distribution of PNH RBCs (percent Type II + III) over time will be plotted by cohort with each subject being identifiable. Subjects who enter both cohorts will be identified in a footnote. A separate plot will be presented for Part 1 and overall i.e. Part 1, 2A, 2B, 2C and 3 combined. A dotted line will be used to identify follow-up (Part 3). The actual sampling day will be used on the x-axis. The plots will include a reference line at Day 1. A reference line at Day 365 will also be added for the plots covering the whole study. These plots will be repeated for Clonal distribution of PNH RBCs (percent Type III), C3d deposition on RBC cells (percent Type II + III) and C3d deposition on RBC cells (percent Type III).

11. SAFETY

11.1. EXTENT OF EXPOSURE

For each subject the following data will be listed:

- Days of dosing in Part 1
- Days of dosing in Part 2A
- Days of dosing in Part 2B
- Days of dosing in Part 2C
- Last study day of dosing
- Compliance for Part 1, 2A, 2B, 2C and overall (excluding Part 2C), based on the percentage of days they took study medication prior to discontinuation/completion.

Compliance is calculated as the number of days the subject took study medication divided by the duration the subject was in the study. If the investigator instructed the subject to stop taking study medication for a period of time e.g. due to an adverse event, then this period will not be included in the denominator for the compliance calculation.

If subjects in Cohort 2 have their dose escalated to 360 mg/day separate information will be supplied for each dose. This will also be done if subjects change their dose for any other reason, with rows of the listing being in chronological order. For those subjects who use the ambulatory syringe pump the first day of using the pump will be listed. The date of change in formulation to acetate-buffered sorbitol will also be listed.

11.2. ADVERSE EVENTS

AEs will be coded using the MedDRA version 21.0.

AEs will be considered treatment-emergent (TEAE) unless there is clear indication that the event occurred prior to first dose of study drug. AEs present prior to the first dose of study drug administration that increased in severity or relationship to study drug after the first dose of study drug and up to 30 days beyond the last dose of study drug will be classed as a TEAE. Events with missing or partial dates will be handled such that in the absence of contradictory information an AE is treatment emergent. So for a missing start date (where stop date is after date of first dose) the date will be imputed as the date of first dose; for a missing stop date the date will be imputed as the last study date. If a partial date is recorded, the following convention will be used to assign the AE:

- If a start date is missing the day information and month/year is the same as first dose date then use first dose date, else '01' will be used for the day; if a start date is missing the month and the year is the same as first dose date then use first dose date, else January will be used for the start month.
- If a stop date is missing the day information and month/year is same as last study date then use last study date, else last day of the given month will be used for the stop day; if a stop date is missing the month and year is the same as last study date then use last study date, else December will be used for the stop month.

Only TEAEs will be included in the summary tables. An overall summary will present the number of subjects by cohort and overall with:

- any TEAE
- any TEAE considered as related to study drug (evaluated by the investigator as Possibly Related or Probably Related or not reported)
- any serious TEAE
- Maximum intensity TEAE of none, mild, moderate, severe ; i.e. a subject with TEAEs at different intensities will be summarized at the most severe intensity
- any TEAE leading to study drug discontinuation
- any TEAE leading to death

The table will also include the total number of TEAEs reported in each cohort and overall. The total number of unique terms within subjects will also be presented, counting each PT only once within each subject.

The number of subjects with TEAEs will be presented by SOC, PT and cohort. Subjects with multiple TEAEs within a SOC or SOC/PT combination will be counted only once for that SOC or SOC/PT combination. Similar summaries will be presented for related TEAEs.

Summaries of TEAEs by maximum intensity (Mild, Moderate, or Severe) will be presented.

All summary tables will be presented by study part, over Parts 1 to 2B (i.e. up to and including Day 365) and over the whole study; where AEs will be categorized by the Part in which the AE started i.e. an AE which began during Part 1 will be categorized under Part 1 even if it continues into Part

2A (unless it increases in severity during Part 2A, when it will be counted in both Parts 1 and 2A). Summaries will be ordered by descending order of total events.

The overall summary will be based on unique subjects, so subjects who enter both cohorts will only be counted once. For subjects who enter both cohorts, AEs reported in Cohort 2 will be assessed for treatment emergence without taking into account AEs reported in Cohort 1.

All TEAEs will be listed by subject and start date. Separate listings of serious TEAEs and TEAEs leading to discontinuation of study drug will also be generated. The listing will also include the onset time since last dose, duration of AE, part of the study the AE started and the part of the study the AE stopped.

11.3. LABORATORY EVALUATIONS

For Cohort 2, observed and change from baseline values will be summarized for all hematology, chemistry and coagulation clinical laboratory parameters using descriptive statistics, by part of the study and study visit.

A shift table from baseline (with marginal totals) of normal, abnormal low, abnormal high and missing records will also be summarised for hematology, chemistry and coagulation clinical laboratory parameters by cohort and study part and study visit, using frequency counts and percentages.

Clinical laboratory data will be listed by cohort. The listing will identify the study part and will include changes from baseline values and values that are outside the reference range will be flagged. Out of range laboratory results with their corresponding changes from baseline will also be listed.

11.4. IMMUNOGENICITY DATA

Immunogenicity data will be listed by cohort.

11.5. VITAL SIGNS

For Cohort 2, observed and change from baseline values will be summarized for all vital signs parameters using descriptive statistics, by part of the study and study visit.

Absolute values and changes from baseline values will be listed by cohort. In the listing, values of potential clinical importance will be flagged. These are defined as:

- Systolic blood pressure ≤80mmHg or ≥165mmHg
- Diastolic blood pressure ≤40mmHg or ≥95mmHg
- Pulse ≤40bpm or ≥120bpm
- Temperature ≥38^{o}C

The number of subjects satisfying each of the criteria specified below will also be summarized for the safety set by cohort and by study part, over Parts 1 to 2B (i.e. up to and including the Day 365 visit) and over the whole study.

Systolic blood pressure:

- all values within 80mmHg and 165mmHg
- at least one value ≤ 80mmHg and none ≥ 165mmHg
- at least one value ≥ 165mmHg and none ≤ 80mmHg
- at least one value ≤ 80mmHg and at least one value ≥ 165mmHg

Diastolic blood pressure:

- all values within 40mmHg and 95mmHg
- at least one value ≤ 40mmHg none ≥ 95mmHg
- at least one value ≥ 95mmHg none ≤ 40mmHg
- at least one value ≤ 40mmHg and at least one value ≥ 95mmHg

Pulse:

- all values within 40bpm and 120bpm
- at least one value ≤ 40bpm and none ≥ 120bpm
- at least one value ≥ 120bpm and none ≤ 40bpm
- at least one value ≤ 40bpm and at least one value ≥ 120bpm

Temperature:

- all values < 38 °C
- at least one value ≥ 38 °C

11.6. ECG

For Cohort 2, observed and change from baseline values will be summarized for all ECG continuous data parameters using descriptive statistics, by part of the study and study visit.

Observed and change from baseline values will be listed by cohort. In the listing, values of potential clinical importance will be flagged. These are defined as:

- QT, QTcB, QTcF ≥450 msec
- QT, QTcB, QTcF increase from baseline ≥30 msec
- PR ≤100msec or ≥240msec
- QRS ≥140msec
- Heart rate ≤40bpm or ≥120bpm

The number of subjects satisfying each of the criteria specified below will also be summarized for the safety set by cohort and by study part, over Parts 1 to 2B (i.e. up to and including the Day 365 visit) and over the whole study.

QT, QTcB, QTcF:

- all values < 450 msec
- at least one value ≥ 450 msec and < 500 msec
- at least one value ≥ 500 msec

and

- all changes from baseline < 30 msec
- at least one change from baseline ≥ 30 msec and < 60 msec
- at least one change from baseline ≥ 60 msec

PR:

- all values within 100msec and 240msec
- at least one value ≤ 100msec and none ≥ 240msec
- at least one value ≥ 240msec and none ≤ 100msec
- at least one value ≤ 100msec and at least one value ≥ 240msec

QRS:

- all values < 140msec
- at least one value ≥ 140msec

Heart rate:

- all values within 40bpm and 120bpm
- at least one value ≤ 40bpm and none ≥ 120bpm
- at least one value ≥ 120bpm and none ≤ 40bpm
- at least one value ≤ 40bpm and at least one value ≥ 120bpm

11.7. PHYSICAL EXAMINATION

Physical examination data will be listed by cohort.

12. INTERIM ANALYSES

The SMC reviewed safety/tolerability, PK and PD data after Part 1 (Day 28) of Cohort 1 was completed. This data was used to decide whether to proceed to Cohort 2 and the dose level to use in Cohort 2. The same review process will be followed if any additional cohorts are added to the study.

In addition, the SMC are responsible for conducting regular (monthly) safety reviews during the treatment phase of the study.

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

An interim report (Dated 18th May 2017) was prepared based on all Cohort 1 subjects and the first 3 subjects enrolled in Cohort 2 (i.e. those recruited under protocol versions up to and including Amendment 4). The interim report included data collected up to the end of Part 2A for subjects who completed Part 2A or to the end of Part 3 if they didn't enter Part 2A. Further reports may be prepared with each report containing cumulative information. These reports will be performed on data that will have been fully checked and considered as final. Any changes to the data previously reported will be fully auditable and discussed in the subsequent reports.

13. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

The changes from the analyses specified in the protocol are:

- Total bilirubin was not included as a secondary endpoint in the protocol but has been included in the SAP so this endpoint can be investigated further. Similarly, PNH granulocytes (percent FLAER) and PNH monocytes (percent FLAER) were not included as PD endpoints in the protocol but have been included in the SAP.
- No formal statistical testing is planned for this study however for Cohort 2 comparisons to baseline will be performed.