STATISTICAL ANALYSIS PLAN

APL-2
PHASE IIa

A Phase IIa, Open Label, Multiple Dose Study to Assess the Safety, Efficacy and Pharmacokinetics of Subcutaneously Administered APL-2 in Subjects with Paroxysmal Nocturnal Hemoglobinuria (PNH)

PROTOCOL IDENTIFIER: APL2-202

Study Sponsor(s): Apellis Pharmaceuticals
6400 Westwind Way,
Suite A,
Crestwood, KY 40014
USA

Author: PPD

Protocol: Version 1.0 (30th November 2017)
Version 2.0 (17th January 2018)
Version 3.0 (31st January 2018)

SAP Version #: 1.0

SAP Date: 17 Jul 2019

Status: Final

Signature Page

Protocol Number:	APL2-202
Protocol Title:	A Phase IIa, Open Label, Multiple Dose Study to Assess the Safety, Efficacy and Pharmacokinetics of Subcutaneously Administered APL-2 in Subjects with Paroxysmal Nocturnal Hemoglobinuria (PNH)
Version:	Final v1.0
Version Date:	17 Jul 2019

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

Author

PPD

PPD

PPD ParamStat Limited

17 JUL 2019
Date (dd-Mmm-yyyy)

Approval

PPD

PPD

Apellis Pharmaceuticals, Inc.

17 JUL 2019
Date (dd-Mmm-yyyy)

PPD

PPD

Apellis Pharmaceuticals, Inc.

17 Jul 2019
Date (dd-Mmm-yyyy)

REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	17 Jul 2019	New Document

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ABBREVIATIONS

AE	Adverse Event
AUC	Area Under the Curve
BLQ	Below Limit of Quantification
CSR	Clinical Study Report
ECG	Electrocardiograms
FACIT	Functional Assessment of Chronic Illness Therapy
ITT	Intent To Treat
LASA	Linear Analog Scale Assessment
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
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
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

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of safety, efficacy and pharmacokinetic/pharmacodynamic data as described in the final study protocol version 3.0 dated 31st January 2018. Specifications for tables, figures, and listings are contained in a separate document. 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).

At the end of 2018 the sponsor took the decision to close enrollment into this study. At this point only 4 subjects had enrolled. These subjects have been allowed to complete the study. As a result only an abbreviated CSR will be produced for this study.

2. OBJECTIVES, ESTIMAND(S), AND ENDPOINTS

2.1 Objectives

The objectives of the study are to assess safety, tolerability, preliminary efficacy and pharmacokinetic (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.

2.2 Estimands

Estimands are not defined due to the decision to close enrollment for this study after only 4 subjects had been enrolled.

2.3 Endpoints

Unless stated otherwise changes from baseline will be calculated taking baseline as the last measurement prior to the first dose of investigational product.

2.3.1 Primary Endpoints

- Change from baseline in lactase dehydrogenase (LDH)
- Change from baseline in haptoglobin
- Change from baseline in hemoglobin.

2.3.2 Secondary Endpoints

- Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale score
- Change from baseline in reticulocyte count
- Change from baseline in total bilirubin
- Number of red blood cell (RBC) transfusions per month
- Change from baseline in Linear Analog Scale Assessment (LASA) for Quality of Life.

2.3.3 Safety Endpoints

- Incidence and severity of treatment-emergent adverse events (TEAEs)
- Changes from baseline in vital signs
- Changes from baseline in laboratory parameters
- Changes from baseline in ECG parameters.

2.3.4 Pharmacokinetic Endpoints

- APL-2 serum concentrations
- PK parameters for APL-2 will be estimated from the individual serum concentration-time data over the whole time period 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 (t) at the end of the study.
$C_{trough,max}$	Maximum observed pre-dose serum concentration, calculated for both 270mg and 360mg where subjects receive both doses.

2.3.5 Pharmacodynamics Endpoints

- Changes from baseline and percentage changes from baseline in complement C3 levels
- Changes from baseline and percentage of baseline in complement CH50 and AP50 levels
- Changes from baseline and percentage changes from baseline in C3 deposition on RBC cells
- Changes from baseline and percentage changes from baseline in Clonal distribution of PNH RBCs

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.

3. STUDY DESIGN

3.1 General Description

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

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

The planned dose for this single cohort study will be a daily dose of 270 mg/day however from Part 2A onwards intra-subject dose escalation up to a dose of 360 mg/day may be permitted. All doses will be administered as SC infusions. APL-2 will be supplied as a sterile solution of APL-2 in acetate-buffered mannitol or in acetate buffered sorbitol, at concentrations of up to 40 mg/mL.

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

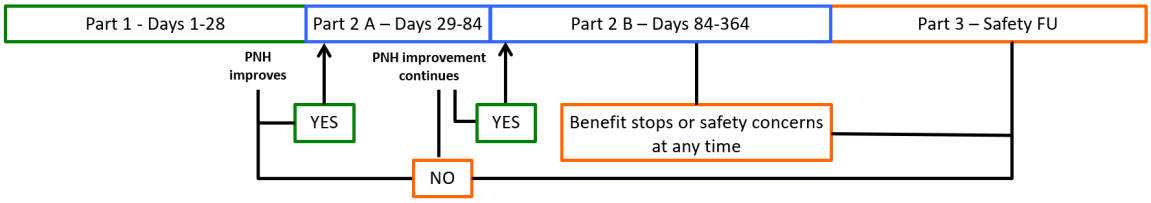
Subjects will be entered into Part 1 of the study on Day 1 at a time designated by the Investigator. Research nurses or other appropriately qualified research personnel will administer the SC infusions for a minimum of 3 days (Days 1-3) until the research nurse

considers that the subject is both capable and confident to conduct self-administration. The subject will continue to self-administer infusions at the clinic on those days when a clinic visit occurs (Day 8, 15 and 22) and at an off-site location convenient to the subject on all other days up to Day 28 in Part 1. Following review of available safety, PK and PD data by the investigator and sponsor subjects demonstrating clinical benefit from the treatment may progress to Part 2A of the study and continue to receive daily doses of APL-2 until Day 84, and then may progress to Part 2B of the study and continue to receive daily doses of APL-2 until Day 364. Doses will be self-administered throughout this period at an off-site location convenient to the subject with the exception of Days 29, 36, 43, 57, 71, 85, 113, 141, 169, 197, 225, 253, 281, 309, and 337 where dosing is performed by the subject at the clinical site. If a subject has a sub-optimal clinical response during daily dosing with 270 mg APL-2, the dose may be increased up to 360 mg/day during part 2A, and doses will be administered at the clinical site every 2 weeks for the first 6 weeks after commencing the higher dose. After the conclusion of the treatment period (Day 364), subjects will enter Part 3 of the study and return to the clinical site for follow-up study procedures on Day 365, 379, and 393 and final study procedures at an Exit Visit on Day 414. If a benefit is observed an extension study will be considered and will be submitted as a further protocol amendment or as a follow-up study

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

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

Continuation of treatment – Decision scheme



3.2 Randomization

Each subject will be assigned a unique identification number upon entering screening. Subjects who complete the study screening assessments and meet all eligibility criteria will be scheduled to enter the study and receive APL-2 treatment.

3.3 Blinding

The study is an open label single treatment arm study and so treatment assignment will not be blinded.

3.4 Sample Size and Power Considerations

The planned sample size was for up to 20 subjects to be enrolled to complete 28 days of dosing. The sample size was considered sufficient to obtain useful safety, tolerability, PD and PK data to support the clinical program. The study was closed for enrollment by the sponsor after 4 subjects were enrolled.

4. STATISTICAL ANALYSIS SETS

4.1 Screened Set

The Screened Set will consist of all subjects who have signed informed consent and are screened for participation in this study. This set will be used only for the purpose of describing subject disposition and for listing the data.

4.2 Safety Set

The Safety Set will consist of all subjects who receive at least one dose of study medication.

4.3 Intent-to-Treat Set

The Intent to Treat (ITT) set will be identical to the Safety Set for this study. All baseline characteristics, demographic and efficacy endpoints data will be presented using the ITT Set.

4.4 Pharmacokinetic Set

The Pharmacokinetic (PK) Set is defined as all subjects in the Safety Set and for whom at least one quantifiable PK sample (i.e. not impacted by any important protocol deviations or other events) post-dose PK measurement (even if below the limit of quantification).

4.5 Pharmacodynamic Set

The Pharmacodynamic (PD) Set is defined as all subjects in the Safety Set with at least one quantifiable (i.e. not impacted by any important protocol deviations or other events) post dose PD evaluation.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

A listing of all Screen Failures (i.e., subjects who were screened but not dosed) will be presented along with reasons for screen fail.

Disposition data, including whether the subject entered Parts 1, 2A, 2B and 3 with the corresponding start dates (and study day) will be listed. If a subject withdrew during the study then the reason for withdrawal will also be listed.

A listing of the analysis sets the subjects are included in will be presented.

5.2 Demographic and Other Baseline Characteristics

Demographic data (gender, race, ethnicity, age [years], weight [kg], height [cm] and BMI [kg/m^2]) will be listed for the Safety Set.

Time since diagnosis of PNH (years) will also be listed.

5.3 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0. Medical history will be listed for the Safety Set.

5.4 Prior Medications

WHO Drug Dictionary Version 2018:03 will be used to classify prior medications by therapeutic class. A prior medication is defined as any medication with the start date prior to the date of the first dose of investigational product.

All prior medications will be listed for the Safety Set.

5.5 Concomitant Medications

WHO Drug Dictionary Version 2018:03 will be used to classify concomitant medications by therapeutic class. A concomitant medication is defined as any medication with the start date prior to the date of the first dose of investigational product and continuing after the first dose of investigational product or with a start date between the dates of the first and last doses of investigational product, inclusive. Medications started before study dosing, but continuing after are considered as both prior and concomitant medications.

All concomitant medications will be listed for the Safety Set.

5.6 Exposure to Investigational Product

All exposure data will be listed for the Safety Set. In addition, 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
- Last study day of dosing

If subjects 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.

5.7 Measurements of Treatment Compliance

Compliance for Part 1, 2A, 2B and overall, based on the percentage of days they took study medication prior to discontinuation/completion will be listed for the Safety Set. Compliance is calculated as the number of days the subject took the investigational product divided by the duration the subject was in the study. If the investigator instructed the subject to stop taking the investigation product 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.

5.8 Protocol Deviations

Protocol deviations will be recorded by the site separately from the clinical database. The CRO/Apellis will classify major and minor protocol deviations per the agreed protocol deviation management plan. The Apellis study team will review the protocol deviations and their classification throughout the study and before database lock.

Confirmed major and minor protocol deviations will be documented in the Protocol Deviation tracker for the study. Major/minor protocol deviations will be listed for the Safety Set.

6. EFFICACY ANALYSES

All efficacy analyses will be based on the ITT Set. For each efficacy variable, the last value collected before the first dose of investigational product will be used as baseline for all analyses of that efficacy variable.

6.1 Analyses of Primary Efficacy Endpoints

Individual LDH, haptoglobin and hemoglobin will be listed together with changes from baseline and percentage changes from baseline by study part and study visit. For LDH the value relative to the upper limit of normal (ULN) (i.e. value/ULN) will also be presented and for haptoglobin and hemoglobin values relative to the lower limit of normal (LLN) (i.e. value/LLN) will also be presented.

Absolute values, changes from baseline and percentage changes from baseline will be summarized, using descriptive statistics, by part of the study and study visit. The number and percentage of subjects ≤1X ULN and ≤ 1.5X ULN for LDH will also be summarized by part of the study and study visit. The number and percentage of subjects ≥ 1X LLN for haptoglobin and hemoglobin will also be summarized by part of the study and study visit.

Absolute values, changes from baseline and percentage changes from baseline will be plotted by study day with each subject being identifiable. A dotted line will be used to identify follow-up (Part 3). The actual sampling day will be used on the x-axis. The changes and percentage changes from baseline plots will include a reference line for 0 on the y-axis.

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 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 (Packed Red Blood Cells [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.

6.2 Analyses of Secondary Efficacy Endpoints

6.2.1 FACIT Fatigue Scale

Absolute FACIT fatigue scores will be listed together with changes from baseline by study part and study visit.

Absolute values and changes from baseline will be summarized, using descriptive statistics, by part of the study and study visit.

Absolute values and changes from baseline will be plotted by study day with each subject being identifiable. A dotted line will be used to identify follow-up (Part 3). The actual sampling day will be used on the x-axis. The change from baseline plots will include a reference line for 0 on the y-axis.

Values of FACIT fatigue scores throughout the study will be plotted against time for each subject 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.

6.2.2 Reticulocytes and Total Bilirubin

Each parameter will be listed together with changes from baseline and percentage changes from baseline by study part and study visit. The value relative to the ULN (i.e. value/ULN) will also be presented.

Absolute values, changes from baseline and percentage changes from baseline will be summarized, using descriptive statistics, by part of the study and study visit. The number and percentage of subjects ≤ 1X ULN and ≤ 1.5X ULN will also be summarized by study visit.

Absolute values, changes from baseline and percentage changes from baseline will be plotted by study day with each subject being identifiable. A dotted line will be used to identify follow-up (Part 3). The actual sampling day will be used on the x-axis. The changes and percentage changes from baseline plots will include a reference line for 0 on the y-axis.

6.2.3 RBC Transfusions

All transfusion data will be listed by study part and study visit.

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

Absolute values for the 3 LASA questions and the combined score (sum of the 3 individual LASA questions) will be listed together with change from baseline by study part and study visit.

Absolute values and changes from baseline will be plotted by study day with each subject being identifiable. A dotted line will be used to identify follow-up (Part 3). The actual

sampling day will be used on the x-axis. The change from baseline plots will include a reference line for 0 on the y-axis.

Values of LASA combined scores throughout the study will be plotted against time for each subject 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.

7. SAFETY ANALYSIS

The safety analysis will be performed using the Safety Set. Safety variables include AEs, clinical laboratory variables, vital signs, and ECG variables. For each safety variable, the last value collected before the first dose of investigational product will be used as baseline for all analyses of that safety variable.

All safety analyses will be conducted according to the treatment the subject actually received.

7.1 Adverse Events

AEs will be coded using MedDRA Version 21.0.

An AE (classified by preferred term) that occurs during the treatment phase will be considered a treatment-emergent AE (TEAE) if it has a start date on or after the first dose of investigational product or if it has a start date before the date of the first dose of investigational product, but increases in severity on or after the date of the first dose of investigational product. If more than one AE with the same preferred term is reported before the date of the first dose of investigational product, then the AE with the greatest severity will be used as the benchmark for comparison to the AEs occurring during the treatment phase under the preferred term. An AE that occurs more than 30 days after the date of the last dose of investigational product will not be counted as a TEAE.

An overall summary of the number of subjects with TEAEs will be presented, including the number and percentage of subjects with any TEAEs, serious TEAEs, TEAEs related to investigational product and TEAEs leading to discontinuation of investigational product.

The number and percentage of subjects reporting TEAEs will be tabulated by system organ class (SOC) and preferred term. TEAEs considered related to investigational product will also be summarized by SOC and preferred term. If more than one AE occurs with the same

preferred term for the same subject, then the subject will be counted only once for that preferred term using the most related occurrence for the summarization by relationship to investigational product.

Summary tables will be presented over the whole study and by study part. 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.

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 duration of AE, the part of the study the AE started and the part of the study the AE stopped.

7.2 Clinical Laboratory Data

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.

All laboratory data will be listed. The listing will include changes from baseline values and values that are outside the reference range will be flagged.

7.3 Vital Signs

Observed and change from baseline values will be listed. In the listing, values of potential clinical significance will be flagged. These are defined in the table below.

Table 1: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign Parameter	Flag	Criteria
		Observed Value
Systolic blood pressure (mmHg)	High	≥165
	Low	≤80
Diastolic blood pressure (mmHg)	High	≥95
	Low	≤40
Pulse rate (beats per minute)	High	≥120
	Low	≤40
Temperature (°C)	High	≥38
	Low	-

7.4 Electrocardiogram (ECG)

Observed and change from baseline values will be listed. In the listing, values of potential clinical significance will be flagged. These are defined in the table below.

Table 2: Criteria for Potentially Clinically Significant ECG Values

Vital Sign Parameter	Flag	Criteria	
		Observed Value	Change from baseline
QT, QTcB, QTcF (msec)	High	≥450	≥30
	Low	-	-
PR (msec)	High	≥240	-
	Low	≤100	-
QRS (msec)	High	≥140	-
	Low	-	-
Heart rate (bpm)	High	≥120	-
	Low	≤40	-

7.5 Other Safety Data

Immunogenicity and physical examination data will be listed.

8. PHARMACOKINETIC ANALYSIS

All PK analyses will be based on the PK Set.

8.1 Handling BLQ Values

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).

8.2 Drug Concentration

Linear and log-linear individual concentration profile plots against time will be produced with each subject being identifiable. A dotted line will be used to identify follow-up (Part 3). The actual sampling day will be used on the x-axis.

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

8.3 Pharmacokinetic Parameters

PK parameters will be listed.

9. PHARMACODYNAMIC ANALYSIS

All PD analyses will be based on the PD Set.

9.1 Handling BLQ Values

If a baseline PD value is zero, then the percentage changes 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.

9.2 Pharmacodynamic Data

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 study part and study visit.

Absolute values, changes from baseline and percentage changes from baseline will be plotted for the complement parameter C3 by study day with each subject being identifiable. A dotted line will be used to identify follow-up (Part 3). The actual sampling day will be used on the x-axis. The changes and percentage changes from baseline plots will include a reference line for 0 on the y-axis.

For the complement parameters CH50 and AP50 only percentage of baseline values will be plotted by study day with each subject being identifiable. 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.

For the complement parameter C3 values throughout the study will be plotted against time for each subject 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 being identifiable. A dotted line will be used to identify follow-up (Part 3). The actual sampling day will be used on the x-axis. 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. A dotted line will be used to identify follow-up (Part 3). The actual sampling day will be used on the x-axis. The plot 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 with each subject being identifiable. A dotted line will be used to identify follow-up (Part 3). The actual sampling day will be used on the x-axis. 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).

10. OTHER ANALYSES

No other analyses are planned for this study.

11. INTERIM ANALYSIS

Data may be reported while the study is ongoing to help guide decisions to further develop APL-2. These reports will be performed on data that will have been fully checked and considered as final. Any changes to the data previously reported will be fully auditable and discussed in subsequent reports.

12. SAFETY MONITORING COMMITTEE

A periodic safety review will take place on a regular basis by the SMC to review safety/tolerability, PK and PD data. The remit, roles and responsibilities of the SMC is specified in a separate SMC charter.

13. DATA HANDLING CONVENTIONS

13.1 General Data Reporting Conventions

Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category. 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.

Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. 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.

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).

All data will be listed. 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. All efficacy, PK and PD listings will present the last dose received prior to the assessment.

13.2 Definition of Baseline

Baseline is defined as the last observed value prior to taking the first dose of investigational product (based on dates or date/times).

13.3 Derived Efficacy Endpoints

FACIT-fatigue scale score

The FACIT Fatigue Scale is a 13 item Likert scaled instrument which is self-administered by the subjects during clinic visits. Subject are presented with 13 statements and asked to indicate their responses as it applies to the past 7 days. The 5 possible responses are ‘Not at all’ (0), ‘A little bit’ (1), ‘Somewhat’ (2), ‘Quite a bit’ (3) and ‘Very much’ (4). With 13 statements the total score has a range of 0 to 52. Before calculating the total score, most responses (all except Answers 5 and 7) are reversed to ensure that the higher score corresponds to a higher quality of life.

Linear Analog Scale Assessment (LASA)

The Linear Analog Scale assessment (LASA) consists of three items asking respondents to rate their perceived level of functioning. Specific domains include activity level, ability to carry out daily activities, and an item for overall QOL. Their level of functioning is reported

on a 0-100 scale with 0 representing “As low as could be” and 100 representing “As high as could be”. In addition to looking at each domain the combined score (range of 0-300) will be determined.

13.4 Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated assessments before the start of investigational product, then the results from the final assessment made prior to the start of investigational product will be used as baseline. All post-baseline assessments will be used for PCS value determination and all assessments will be presented in the data listings.

13.5 Handling of Missing, Unused, and Spurious Data

13.5.1 Missing Data Imputation for Efficacy Endpoints

No imputation of missing data will be performed.

13.5.2 Missing Date of Investigational Product

When the date of the last dose of investigational product is missing for a subject in the Safety Set, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last known date when investigational product was taken will be used in the calculation of treatment duration.

13.5.3 Missing Date Information for Prior or Concomitant Medications (Therapies/Procedures)

For prior or concomitant medications incomplete (i.e., partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

For a missing start date (where stop date is after first dose of investigational product or missing) the date will be imputed as the first dose date of investigational product; for a missing stop date the date will be imputed as the last study date.

The original data will always be presented in the listings.

13.5.3.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

13.5.3.1.1 Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

13.5.3.1.2 Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

13.5.3.1.3 Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the first dose of investigational product or if both years are the same but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the date of the first dose of investigational product or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

13.5.3.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of investigational product is missing, then replace it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

13.5.3.2.1 Missing Day and Month

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of investigational product, then the day and month of the date of the last dose of investigational product will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then 31 December will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then 01 January will be assigned to the missing fields.

13.5.3.2.2 Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

13.5.3.2.3 Missing Day Only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the date of the last dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the last dose of investigational product or if both years are the same but the month is before the month of the date of the last dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the last dose of investigational product or if both years are the same but the month is after the month of the date of the last dose of investigational product, then the first day of the month will be assigned to the missing day.

13.5.4 Missing Date Information for Adverse Events

For AEs with partial start dates, non-missing date parts will be used to determine if the AE is treatment-emergent or not and for the calculation of study onset day, study stop day and duration. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to study drug administration, e.g. AE start year and month are the same as the year and month of the first dose of investigational product, then the AE will be classified as treatment-emergent.

To facilitate categorization of AEs as treatment emergent, imputation of dates can be used. For AEs, the default is to only impute incomplete (i.e., partially missing) start dates. Incomplete stop dates may also be imputed when calculation of the duration of an AE is required per the protocol. If imputation of an incomplete stop date is required, and both the start date and the stop date are incomplete for a subject, impute the start date first.

For a missing start date (where stop date is after first dose of investigational product or missing) the date will be imputed as the first dose date of investigational product; for a missing stop date the date will be imputed as the last study date.

The original data will always be presented in the listings.

13.5.4.1 Incomplete Start Date

Follow the same rules as in Section 12.4.3.1.

13.5.4.2 Incomplete Stop Date

Follow the same rules as in Section 12.4.3.2.

13.5.5 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of investigational product, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of investigational product, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

13.5.6 Missing Relationship to Investigational Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of the first dose of investigational product, a causality of "Related" will be assigned. The imputed values for relationship to investigational product will be used for incidence summaries, while both the actual and the imputed values will be presented in data listings.

14. ANALYSIS SOFTWARE

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® on a suitably qualified environment.

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

15. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

Due to the decision to close enrollment for this study after 4 subjects had enrolled only a subset of the analyses documented in the protocol are required for reporting. As a consequence the SAP only specifies the analyses required for the abbreviated CSR.

17. APPENDICES

17.1 Schedule of Activities

Study Period	Part 1 – Treatment (Daily from Day 1 to Day 28)										
Study Week	-4	1				2		3		4	
Study Day	-30	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, 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.	x	x				x		x		x	
Coagulation profile	x	x				x		x		x	
Complement profile (C3, CH50 and AP50)	x	x				x		x		x	
Flow cytometry for PNH/C3 deposition	x	x				x		x		x	
Plasma Hb	x	x				x		x		x	
Pregnancy (B-human chorionic gonadotropin)	x										
Urine pregnancy test. J		x				x		x		x	
FACIT fatigue Scale		x						x			
LASA QoL		x						x			
Adverse events		x	x	x	x	x	X	x	X	x	x
Thrombosis record (MAVE). K		x	x	x	x	x	X	x	X	x	x

See footnotes below continuation flow chart

Study Period	Part 2A - Treatment (Daily from Day 29 to Day 84)									
Study Week	5		6		7 and 8		9 and 10		11 and 12	
Study Day	29	30 to 35	36	37 to 42	43	44 to 56	57	58 to 70	71	72 to 84
Informed Consent										
Demographics										
Medical, transfusion, and thrombosis history										
Vaccination. A										
Review entry criteria										
Preventive antibiotic. B	X	X	X	X	X	X	X	X	X	X
Physical examination. C	X						X			
12-lead electrocardiogram. D	X		X		X		X		X	
APL-2 administration. E	S	H	S	H	S	H	S	H	S	H
Injection site assessment. F	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Vital sign measurements. G	X	X	X	X	X	X	X	X	X	X
Urinalysis	X		X		X		X		X	
Blood. I	X		X		X		X		X	
Pharmacokinetics. I	X				X				X	
Anti-APL-2 Ab assay	X								X	
Hematology and chemistry.	X		X		X		X		X	
Coagulation profile	X		X		X		X		X	
Complement profile (C3, CH50 and AP50)	X		X		X		X		X	
Flow cytometry for PNH/C3 deposition	X		X		X		X		X	
Plasma Hb	X		X		X		X		X	
Urine pregnancy test. J	X		X		X		X		X	
FACIT fatigue Scale	X				X				X	
LASA QoL	X				X				X	
Adverse events	X	X	X	X	X	X	X	X	X	X
Thrombosis record (MAVE). K	X	X	X	X	X	X	X	X	X	X

See footnotes below continuation flow chart

Study Period	Part 2B - Treatment (Daily from Day 85 to Day 364) (L)											
Study Week	13 to 16		17 to 20		21 to 24		25 to 28		29 to 32		33 to 36	
Study Day	85	86 to 112	113	114 to 140	141	142 to 168	169	170 to 196	197	198 to 224	225	226 to 252
Vaccination	X											
Preventive antibiotic. B	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination. C	X											
12-lead electrocardiogram. D	X		X		X		X		X		X	
APL-2 administration. E	S	H	S	H	S	H	S	H	S	H	S	H
Injection site assessment. F	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Vital sign measurements. G	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X		X		X		X		X		X	
Blood. I	X		X		X		X		X		X	
Pharmacokinetics. I	X		X		X		X		X		X	
Anti-APL-2 Ab assay	X				X				X			
Hematology and chemistry.	X		X		X		X		X		X	
Coagulation profile	X		X		X		X		X		X	
Complement profile (C3, CH50 and AP50)	X		X		X		X		X		X	
Flow cytometry for PNH/C3 deposition	X		X		X		X		X		X	
Plasma Hb	X		X		X		X		X		X	
Urine pregnancy test. J	X		X		X		X		X		X	
FACIT fatigue Scale	X				X				X			
LASA QoL Scale	X				X				X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Thrombosis record (MAVE) K	X	X	X	X	X	X	X	X	X	X	X	X

See footnotes below continuation flow chart

Study Period	Part 2B - Treatment (Daily from Day 85 to Day 364) (L)							
Study Week	37 to 40		41 to 44		45 to 48		49 to 52	
Study Day	253	254 to 280	281	282 to 308	309	310 to 336	337	338 to 364
Informed Consent								
Review entry criteria								
Preventive antibiotic. B	X	X	X	X	X	X	X	X
Physical examination. C	X						X	
12-lead electrocardiogram. D	X		X		X		X	
APL-2 administration. E	S	H	S	H	S	H	S	H
Injection site assessment. F	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Vital sign measurements. G	X	X	X	X	X	X	X	X
Urinalysis	X		X		X		X	
Blood. I	X		X		X		X	
Pharmacokinetics. I	X		X		X		X	
Anti-APL-2 Ab assay	X				X			
Hematology and chemistry.	X		X		X		X	
Coagulation profile	X		X		X		X	
Complement profile (C3, CH50 and AP50)	X		X		X		X	
Flow cytometry for PNH/C3 deposition	X		X		X		X	
Plasma Hb	X		X		X		X	
Urine pregnancy test. J	X		X		X		X	
FACIT fatigue Scale	X				X			
LASA QoL Scale	X				X			
Adverse events	X	X	X	X	X	X	X	X
Thrombosis record (MAVE). K	X	X	X	X	X	X	X	X

See footnotes below continuation flow chart

Study Period	Part 3 – Follow-up and Exit. (M)			
Study Week	53	55	57	60
Study Day	365	379	393	414
Informed Consent				
Review entry criteria				
Preventive antibiotic. B	X	X		
Physical examination. C	X			X
12-lead electrocardiogram. D	X			
APL-2 administration. E				
Injection site assessment. F	X			
Concomitant medications	X	X	X	X
Vital sign measurements. G	X	X	X	X
Urinalysis	X	X	X	X
Blood. I	X	X	X	X
Pharmacokinetics. I	X	X	X	X
Anti-APL-2 Ab assay	X			X
Hematology and chemistry.	X	X	X	X
Coagulation profile	X	X	X	X
Complement profile (C3, CH50 and AP50)	X	X	X	X
Flow cytometry for PNH/C3 deposition	X	X	X	X
Plasma Hb	X	X	X	X
Urine pregnancy test. J	X		X	X
FACIT fatigue Scale	X		X	X
LASA QoL Scale	X		X	X
Adverse events	X	X	X	X
Thrombosis record (MAVE) K	X	X	X	X

See study flow chart footnotes on next page

FOOTNOTES:

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

B. Preventive antibiotics will be prescribed from Day 1. Antibiotics will be taken from Day 1 until 14 days after the first dose of APL-2. Specifically:
   - Day 1 to Day 14: Ciprofloxacin 500 mg twice daily (take post dose ECG before Ciprofloxacin is administered on days 1).
   - 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.

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. At clinic visits, vital signs will be measured within 2 hours prior to dosing and within 30 minutes after dosing. When 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. If done on a dosing day, urine pregnancy test should be completed for WOCBP prior to dosing.

K. MAVE = Major Adverse Vascular Event. Ambulatory syringe infusion pump training will include instructions to report any events to the PI.

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

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