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Statistical Analysis Plan

Study Title:	An Open Label, Prospective, Study to Assess the Safety, Tolerability, Efficacy and Pharmacokinetics of APL-2 in Patients with Warm Antibody Autoimmune Hemolytic Anemia (wAIHA) or Cold Agglutinin Disease (CAD)
Protocol Number:	APL2-CP-AIHA-208
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1. LIST OF ABBREVIATIONS AND ACRONYMS

Abbreviations and Acronyms	Description
°C	Degrees Celsius
ADaM	Analysis Data Model
ADDV	ADaM Data Structure for Protocol Deviation Analysis
ADPC	ADaM Data Structure for Pharmacokinetic Concentrations Analysis
ADPP	ADaM Data Structure for Pharmacokinetic Parameters Analysis
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIHA	Autoimmune Hemolytic Anemia
ATC	Anatomical Therapeutic Chemical
CAD	Cold Agglutinin Disease
BLQ	Below the Limit of Quantification
bpm	beats per minute
CFB	Change From Baseline
$C_{trough, max}$	Maximal Trough Concentration
CS	Clinically Significant Abnormality
DPC	DP Clinical Inc.
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ET	Early Termination
ETFU	Early Termination Follow-up
FACIT	Functional Assessment of Chronic Illness Therapy
HiB	Haemophilus Influenzae Type B
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ITT	Intent-to-Treat
LASA	Linear Analog Scale Assessment
LDH	Lactate Dehydrogenase

Abbreviations and Acronyms	Description
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeters of Mercury
msec	Milliseconds
NCS	Not Clinically Significant
ODS	Output Delivery System
QC	Quality Control
QoL	Quality of Life
QtC	Corrected QT interval
QTcB	Bazett's QT Interval Correction
QTcF	Fridericia's QT Interval Correction
PRBC	Packed Red Blood Cell
PCFB	Percent Change From Baseline
PCV13	Pneumococcal Conjugate Vaccine
PD	Pharmacodynamics
PI	Principal Investigator or Designee
PK	Pharmacokinetics
PP	Per Protocol
PPSV23	Pneumococcal Polysaccharide Vaccine 23
PT	Preferred Term
RBC	Red Blood Cell
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
TLFs	Tables, Listings and Figures

Abbreviations and Acronyms	Description
wAIHA	Warm Antibody Autoimmune Hemolytic Anemia
WHO	World Health Organization
WHODrug	World Health Organization Drug Dictionary
WOCBP	Woman of Childbearing Potential

2. INTRODUCTION

This Statistical Analysis Plan (SAP) is prepared to provide a more technical and detailed elaboration of the principal statistical features stated in the protocol. The SAP will ensure that the tables, listings, and figures that will be produced and statistical methods that will be used are complete and accurate and will allow valid conclusions to be drawn. In the development of this SAP, the following study documents were used:

- Protocol Number (Version 1.0 Amendment 4), 17 Jan 2019
- Electronic Case Report Form (eCRF), 09 Mar 2019
- Medical Coding Guidelines (Version 2.0), 02 Nov 2017

The principles in the following guidance documents are followed in the preparation of this SAP:

- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E3 (ICH 1995): Structure and Content of Clinical Study Reports
- ICH E6 R2 (ICH 2016): Guideline for Good Clinical Practice - Integrated Addendum to ICH E6 (R1).
- ICH E9 (ICH 1998): Statistical Principles for Clinical Trials

In the event that a discrepancy is found between the descriptions in the statistical section of the protocol and this document, the description in this document supersedes the descriptions in the statistical section of the protocol. Any deviations from the final analysis plan or from what is outlined in the protocol will be discussed in the final study report.

3. STUDY OVERVIEW

This study is being conducted as part of a series of studies for the clinical development of APL-2. This study will be the initial exploration of APL-2 in patients with a primary diagnosis of Warm Antibody Autoimmune Hemolytic Anemia (wAIHA) who relapsed from, did not respond to, or did not tolerate at least one prior wAIHA treatment regimen (such as prednisone, rituximab, or splenectomy), or a primary diagnosis of Cold Agglutinin Disease (CAD) regardless of prior treatment history.

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 a primary diagnosis of wAIHA who relapsed from, did not respond to, or did not tolerate at least one prior wAIHA treatment regimen (such as prednisone, rituximab, or splenectomy), or a primary diagnosis of CAD regardless of prior treatment history.

An exploratory objective of the study is to assess the pharmacodynamics (PD) of multiple SC doses of APL-2 when administered to wAIHA and CAD patients.

3.2 Study Endpoints

3.2.1 Primary Safety Endpoint

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

3.2.2 Efficacy Endpoints

- Change from baseline in hemoglobin
- Number of red blood cell (RBC) transfusions during the study
- Change from baseline in absolute reticulocyte count
- Change from baseline in lactate dehydrogenase (LDH)
- Change from baseline in haptoglobin
- Change from baseline in indirect bilirubin

- APL-2 serum concentrations and PK parameters, as appropriate
- Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT) scale and the Linear Analog Scale Assessment scale (LASA) including energy level, ability to perform daily activity, and overall quality of life (QoL)

3.2.3 Exploratory Study Endpoints

Exploratory PD markers include:

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

3.3 Study Design

This is a Phase II, open-label, prospective pilot study of APL-2 conducted in subjects with a primary diagnosis of wAIHA or CAD in parallel. The study will consist of up to 24 subjects, a target of 12 subjects with a primary diagnosis of wAIHA in Cohort 1 and a target of 12 subjects with a primary diagnosis of CAD in Cohort 2. Subjects will be randomized 1:1 to a 270mg or 360mg daily SC APL-2 dosage group within each cohort for up to 12 months (Part A, the Core Study Phase).

Following Day 336 and the completion of the Part A Core Study Phase, subjects will be eligible to participate in Part B, a Long-Term Extension Phase, in order to continue to receive treatment with APL-2. The Long-Term Extension Phase is described later in this section.

Through Part A (Day 336), dose escalation from 270 mg/d to 360 mg/d, or de-escalation from 360 mg/d to 270 mg/d may occur after a thorough evaluation of available safety and laboratory assessment.

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.

Part A: Core Study Phase:

Screening will take place within 30 days prior to the start of dosing on Day 1. If needed (see inclusion criteria), *Neisseria meningitides* types A, C, W, Y and B (administered as two separate vaccines), Pneumococcal Conjugate Vaccine (PCV13) or Pneumococcal Polysaccharide Vaccine 23 (PPSV23), and Haemophilus Influenzae Type B (Hib) vaccinations will be administered prior to dosing on Day 1.

Subjects who meet all the inclusion criteria and none of the exclusion criteria will be enrolled into the study on Day 1 at a time designated by the Principal Investigator or designee (PI). During study, the first 3 daily SC doses of APL-2 (Day 1 to 3) as well as doses on Day 7 and Day 14 will be administered at the clinical site. From Day 4 to Day 336 daily doses of APL-2 will be administered off-site by a study nurse or self-administered by the subject and/or caregiver, at the subject's home, workplace, or other location convenient to the subject with the exception of those days where dosing is at the clinical site. At any time during the study, if subjects discontinue treatment, or if after the conclusion of the Part A Core Study Phase a subject does not elect to enter the Part B Long-Term Extension Phase, subjects will return to the clinical site for safety follow-up study procedures after 6 weeks, followed by final study procedures at an Exit Visit after another 6 weeks. See Study Flowchart in Section 3.3.2.

The planned length of participation in the study for each subject is at least approximately 450 days (from Day –30 through completion of the Day 420 Exit visit procedures [for subjects that do not elect to enter the Part B Long-Term Extension Phase]). Subjects that continue in the Part B Long-Term Extension Phase may continue to receive treatment indefinitely until the subject discontinues or the development program is terminated. The study duration may change in the event that the study is terminated early, additional subjects are needed, additional time is required to review safety between groups, or extended safety and PK sampling is added for a dose group (e.g. beyond Day 420).

Part B: Long-Term Extension Phase:

Following Visit 15 (Week 48), subjects who elect to continue in the Part B Long-Term Extension Phase will return to the site at 12-week intervals indefinitely until the subject discontinues or the development program is terminated.

Specific procedures for each visit are listed in the Study Flow Chart for the Long-Term Extension Phase in Table 2 in Section 3.3.2.

At Visit 15 (Week 48), subjects electing to enter the Part B Long-Term Extension Phase will begin an APL-2 dose regimen of APL-2 1,080 mg twice weekly (with potential to escalate to APL-2 1,080 mg every 3 days). When switching from the Part A Core Study Phase formulation and dose of APL-2 (270 mg/d or 360 mg/d) to the formulation and dose intended for use in the Long-Term Extension Phase (APL-2 1,080 mg twice weekly), subjects should return to the site for APL-2 administration training and to conduct Dose Transition Visits 1, 2 and 4 weeks after the new dose is initiated and perform the procedures outlined in Appendix Section 8.1.

Subjects who plan on continuing in the Part B Long-Term Extension Phase should be instructed to skip their daily Part A Core Study Phase Dose the day prior to Visit 15 (i.e., the subject should not self-administer APL-2 on Day 335).

Note: The first dose of APL-2 1,080 mg should be administered at the Visit 15 (Day 336), with Dose Transition Visits at Week 49, Week 50, and Week 52. Some subjects may enter the Part B Long-Term Extension Phase prior to the availability of the sorbitol formulation. These subjects should continue on their Part A Core Study Phase dose into the Part B Long-Term Extension Phase. These subjects will transition to the Long-Term Extension Phase dose at the next scheduled visit at which the sorbitol formulation and dose is available, and should schedule Visits T1, T2, and T3 1, 2 and 4 weeks following the visit at which the sorbitol dose is initiated. These subjects should be instructed to skip their Part A dose the day before the visit at which the APL-2 1,080 mg twice weekly dose regimen is scheduled to be initiated.

Subjects who discontinue treatment early should complete one Early Termination Follow-up Visit (ETFU) 6 weeks after discontinuation of treatment, and one Early Termination (ET) Exit Visit 6 weeks after the ETFU as outlined in Appendix 8.1.

Study Assessments align with those conducted in the Core Study Phase and are described in Section 13 of the Clinical Study Protocol (Version 1.0 Amendment 4), 17 Jan 2019.

3.3.1 Sample Size Considerations

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

3.3.2 Study Assessments Schedules

Study assessments are described in detail in Section 12.0 of the protocol (Version 1.0 Amendment 4), and summarized in Study Flow Charts for Part A and Part B in Appendix Section 8.1.

4. GENERAL CONSIDERATIONS

4.1 Definitions

4.1.1 Study Day

Study Day 1 will be the day a subject takes the first dose of APL-2. Study days will be calculated as:

For events that occurred on the day of or after administration of the first APL-2 dose:

Study Day = visit date – date of first APL-2 dose + 1

For events that occurred on days before administration of the first APL-2 dose:

Study Day = visit date – date of administration of first APL-2 dose

4.1.2 Visit Windowing Based on Study Day

Data will be summarized and analyzed based on the list of visits specified in table below for the Part A Core Study Phase. The relative day will be used to assign analysis visit following the table below. All the records post-baseline will be assigned to an appropriate analysis visit using the following:

For the post-baseline visits, the lower and the upper bound for the analysis visit windows are defined as the midpoints of the target date of the scheduled visits. If the date of assessment falls in between the lower bound and the upper bound for a visit as specified in the schedule of assessments of the protocol, then it will be assigned to that visit. If the interval separating 2 scheduled visits is an even number of days, the middle day will be included in the lower bound of the next visit. If more than 1 record is within the same analysis visit window, the record closest to the midpoint of the interval will be used in the analysis. If 2 records are tied before and after the middle of the interval, the earlier record will be used in the analysis. 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.

In listings that are presented by visit, windowed assessments that are used in the analysis tables by visit will be identified.

Part	Study Visit	Target Day	Analysis Window	Interval
Core Study Phase (Part A)	1	-30	<1*	NA
	2	1	1	1
	3	2	2	1
	4	3	3	1
	5	7	>=4- < 11	7
	6	14	11– < 21	10
	7	28	21- < 42	21
	8	56	42 - <70	28
	9	84	70 - < 98	28
	10	112	98 - < 126	28
	11	140	126 - < 154	28
	12	168	154 - < 196	42
	13	224	196 - < 252	56
	14	280	252 - < 308	56
	15	336	308 - < 364	56
	16 (FU)	378	364 - < 399	35
	17 (Exit)	420	399 - < 441	42

*Must be prior to dosing if time of assessment is recorded.

4.1.3 Baseline and Change from Baseline

In general, the baseline for this study (with the exception of physical examination) will be taken as the latest pre-dose measure on Study Day 1 (i.e. prior to the first dose for all cohorts). 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 physical

examination, the baseline assessment will be considered as the Screening Visit 1.

Unless indicated otherwise change from baseline (CFB) will be calculated as follows:

CFB = Visit Result – Baseline Result

Percent change from baseline (PCFB) will be calculated as follow:

PCFB (%) = 100(Visit Result – Baseline Result)/Baseline Results*

4.2 Analysis Sets

After all the data have been verified/coded/entered into the database, a review will be performed by DP Clinical, Inc (DPC) and the sponsor. The purpose of this review will be to define the analysis sets. The review will also check the quality of the data, identifying outliers, and making decisions on how to deal with problems in any data (e.g., missing values, withdrawals, protocol deviations). After the pre-analysis review, resolution of all issues and documentation of all decisions, the database will be locked.

Screened Set:

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

Safety Population / Intent-to-Treat (ITT) Set:

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

Per Protocol (PP) Set:

The PP Set will include subjects who complete Part A Core Study Phase (Visit 15) and who have not violated any inclusion or exclusion criteria and/or deviated from the protocol in a way that could influence their efficacy assessment through Visit 15. Decisions concerning the exclusion of subjects from this set will be made and documented during an adjudication by DPC and the sponsor prior to database lock. Baseline characteristics, demographics and efficacy endpoint data will be presented using the PP Set.

Pharmacokinetic (PK) Set:

The PK Set will include all subjects in the Safety Set who have at least one evaluable non-BLQ post-dose PK measurement.

Pharmacodynamic (PD) Set:

The PD Set will include all subjects in the Safety Set who have at least one evaluable post-dose PD measurement.

4.3 Test Hypothesis and *P*-Value Justification

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

4.4 Procedures for Handling Missing Data and Dropouts

A missed visit and assessment details eCRF page will summarise which visits / assessments were missed along with the reason (e.g., COVID-19, or other). This will be listed for both Part B and Overall Study.

4.4.1 Safety Data

Where appropriate, screening values may be used as baseline in the event of missing or unusable Day 1 measurements. No imputation of missing data for early terminations will be performed.

However, both partial and completely missing dates/times that are not related to early terminations, in addition to missing safety data (e.g., missing severities) will be reviewed on a case by case basis for potential imputations. As a general

rule, a conservative approach will be adopted as outlined in Section 5.2.1 (e.g. partial Adverse Event (AE) onset dates and missing severities will be taken as the earliest 'on treatment' start date and highest severity, respectively, consistent with the partial information available). Moreover, the original data, without imputations, will be presented separately in data listings.

For safety lab parameters that are below or above the limit of quantification, the data will be presented as-is in the listings, but the limit of quantification will be used for the purposes of calculating change from baseline.

4.4.2 PK and Efficacy/PD Concentration Data

APL-2 concentrations reported from pre-dose on Day 1 to the time of the first quantifiable value will be taken as zero for linear plots and the calculation of PK parameters, and equal to the lower limit of quantification (LLOQ) for semi-logarithmic plots.

After this time point, concentrations below the limit of quantification (BLQ) will be set to zero, with the exception of the calculation of the geometric mean where the LLOQ will be used.

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

In the event of a missing PD baseline value a screen measurement or pre-dose unscheduled measurement may be used (whichever is closer to the baseline date).

If a baseline PD value is zero, then the percent change from baseline will not be calculated. If a post baseline value is BLQ, then the value will be set to the LLOQ. Similarly, for PD plots, a BLQ value will be set equal to LLOQ.

4.5 Interim Analysis

One interim analysis is planned when all subjects enrolled in the study have completed Part A, the Core Study Phase (screening to day 336) or discontinued prior to Day 336. The interim analysis will present all planned tables, listings, and figures (TLF) listed in Appendix 8.1 for only the Part A Core Study Phase. The data will consist of:

- For subjects who rollover into the Part B Extension Phase, all data collected through the date of Visit 15 will be included. For occurrence data, such as Adverse Events and Concomitant Medications, records with a start date on or before the Visit 15 (which is considered the start of dosing date for the extension phase) will be included.
- For all subjects who do not rollover into the Part B extension Phase (i.e. who discontinue during the Part A Core Study Phase), all data will be included.

4.6 Subgroup Analysis

Due to the small sample size of the study, no subgroup analyses will occur.

4.7 Multi-Center Studies and Pooling of Centers

This is a multi-center study. Due to the small number of subjects at each site, no adjustments will be made for study site.

5. STATISTICAL ANALYSIS METHODOLOGY

In general, tables will be presented by randomized dose level within cohort (270 mg vs. 360 mg) and by cohort.

Tabulations for continuous data will use a standard set of descriptive statistics: number of observations available (n), mean, standard deviation (SD), median, and range (minimum, maximum).

Categorical or dichotomous data will be tabulated using frequencies (counts and percentages). The numerator and denominator for each percentage calculation will be specified in the footnotes of table shells.

Data listings will present all information recorded in eCRFs for all subjects and visits. All listings will be sorted by cohort and subject number.

Unless otherwise noted, tabulations or descriptive statistics by visit during the Part A Core Study Phase will include only scheduled visits through Visit 15 (i.e. summary statistics will not include follow-up Visits 16 and 17.

5.1 Study Subjects

5.1.1 Subject Disposition

The following disposition categories will be tabulated by randomized dose level within cohort (for categories after enrollment) and by cohort:

- Number of subjects screened
- Number of screen failures with reason for screen failure
- Number of subjects who receive at least at least one dose of APL-2
- Number of subjects with at least1 non-BLQ post-dose PK assessment
- Number of subjects with at least 1 post-dose PD assessment
- Number of subjects who complete Part A Core Study Phase – subjects who complete through Visit 15
- Number of subjects in the PP set per definition in Section 4.2

- Number of early termination subject during Part A Core Study Phase with reason for early termination – subjects who do not complete Visit 15
- Number of subjects who rollover to Part B Long Term Extension Phase
- Reason for Withdrawal during Part B Long Term Extension Phase (Final Analysis Only)

5.1.2 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedure defined in the protocol.

The following categories will be used to group protocol deviations:

1. Eligibility Not Met
2. Study Assessment Noncompliance
3. Study Drug Noncompliance
4. Study Schedule Noncompliance
5. Other

The following are categorical reasons used to document why a protocol deviation occurred:

1. Subject Illness
2. Subject Unable to Comply
3. Subject Refusal
4. Clinical/Site Error
5. Laboratory Error
6. Investigator/Staff decision
7. Other

Subsets of the protocol deviations can be identified as major and minor protocol deviation as described below:

Major Protocol Deviation: A protocol deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

Minor Protocol Deviation: A protocol deviation that will not significantly affect the completeness, accuracy, and/or reliability of the study data and that will not significantly affect a subject's rights, safety, or well-being.

Upon soft lock of database, all documented protocol deviations in the study will be reviewed to identify all major and minor protocol deviations by a data review team including representatives from DPC clinical operations, medical, data management, and statistics, and sent to the sponsor for approval. Final decisions will be documented and incorporated into the ADaM Data Structure for Protocol Deviation Analysis (ADDV) dataset.

Protocol deviation data will be presented for the safety set. Protocol deviation data will be listed. Additionally, the number of deviations and number/proportion of subjects with protocol deviations and with major protocol deviations will be tabulated by randomized dose level and by cohort. The number of deviations and number/proportion of subjects with each protocol deviation category will also be tabulated by randomized dose level and by cohort.

5.1.3 Medical and Surgical History

All medical/surgical history data and ongoing medical history will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 System Organ Class (SOC) and Preferred Term (PT) and by randomized dose level and by cohort.

5.1.4 Prior and Concomitant Medications

Prior and concomitant medications will be coded to the therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug Dictionary (WHODrug) classifications version March 2017.

Prior medications will include any medications reported with a start date prior to the subject taking their first study dose and will be summarized by WHODrug Anatomical Therapeutic Chemical (ATC) Class 3 Term and WHODrug Preferred Name. Concomitant medications will include any medications being taken after the subject starts their study medication and will also be summarized by WHODrug ATC Class 3 Term and WHODrug Preferred Name. Hence, medications ongoing at the start of dosing will be counted in both the prior and concomitant medication summaries.

For the purposes of determining prior and concomitant medications, if a partial date is recorded, the following convention will be used to assign the medication dates:

- 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.

All prior medications and concomitant medications, interventions and procedures will be summarized in listings. The frequency of subjects taking prior medications and concomitant medications will be tabulated

by WHODrug ATC Class 3 and Preferred Name, and by randomized dose level and by cohort.

5.1.5 Exposure

All study drug exposure data will be listed based on the Study Drug Administration eCRF.

For the Part A Core Study Phase, compliance will be calculated as:

$$Compliance = \frac{number\ of\ complete\ study\ doses\ administered\ during\ Part\ A}{total\ expected\ study\ dosesduring\ Part\ A} x\ 100$$

Unless otherwise noted, during the Part A Core Study Phase, the number of expected doses is the number of days during Part A.

For the Part B Long Term Extension Phase, compliance will be calculated as:

$$Compliance = \frac{number\ of\ complete\ study\ doses\ administered\ during\ Part\ B\ prior\ to\ study\ discontinuation/completion}{total\ number\ of\ expected\ study\ doses\ during\ Part\ B} x\ 100$$

where the total number of expected study doses will be based on the time a subject is assigned to the twice weekly dosing schedule and the every-three-days dosing schedule during Part B.

For total on-study time, compliance will be calculated as:

$$Compliance = \frac{number\ of\ complete\ study\ doses\ administered\ prior\ to\ study\ discontinuation}{total\ number\ of\ expected\ study\ doses\ prior\ to\ study\ discontinuation} x\ 100$$

Compliance during Part A, Part B, and total on-study time will be listed by subject. Additionally, exposure and compliance will be summarized for Part A, Part B, and total time on study using descriptive statistics by randomized dose level and by cohort.

5.2 Safety Analysis

The primary objective of the study is to assess the safety and tolerability of APL-2. The safety analyses will be performed on the safety set.

5.2.1 Adverse Events

TEAEs are defined as those AEs that occur after Dosing on Day 1, or worsen in severity, and up to 30 days after the last dose of APL-2. For subjects who rollover to Part B long term extension phase, any AE recorded on the date of Visit 15 (start of dosing for the extension phase) will be included in Part A. Version 20.0 of MedDRA will be used to classify all AEs.

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.

Adverse Events of Special Interest

Adverse events of special interest (AESI) include the following:

- Haemolysis / Haemolytic Anaemia
- Infection
- Thrombosis
- Hypersensitivity
- Clinically Significant Decrease in kidney function
- Injection Site reactions

AESIs will be determined by a review of all AEs by the clinical and data management study staff. This review will allow for the inclusion of AEs of special interest arising during the study that are not on the above list, based on a clinical decision. It is expected that documentation of the AEs of special interest will be maintained outside the Medrio database system by the biostatistics and data management staff (with review by medical) and used by the programmer for analysis of the AEs of special interest.

Adverse Events Summary

An AE data listing of all AEs collected on study, including verbatim term, preferred term, treatment, severity, and relationship to treatment will be provided. Serious Adverse Events (SAEs), adverse events of special interest, and details of subjects withdrawing due to adverse

events will also be listed. The start day (relative to the first dosing day), and the duration of AEs will be included in listings.

A topline summary for Part A, Part B, and Overall will present the number of events and the number of subjects by randomized dose level and by cohort with:

- any TEAE
- any TEAE considered as related to study drug (evaluated by the investigator as Unlikely Related, Unrelated, Possibly Related, Probably Related, Definitely Related, or Unknown)
- any serious TEAE
- Maximum severity TEAE of mild, moderate, severe, life threatening, and death; i.e. a subject with TEAEs at different intensities will be summarized at the most severe intensity
- any TEAE of special interest
- 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 TEAE only once within each subject.

Additionally, the following will be tabulated with the number of events and the number/percent of subjects by randomized dose level in each cohort, and by cohort. Summaries will be ordered by descending order of event count in the overall column. All summary tables will be presented by study part 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 the Part A Core Study Phase will be categorized under Part A even if it continues into Part B (unless it increases in severity).

- TEAEs by SOC and preferred term
- TEAEs by preferred term

- TEAEs regarded as at least possibly related to study drug by SOC and preferred term

The following will also be tabulated with the number/percent of subjects by randomized dose level in each cohort and by cohort:

- TEAEs and Serious AEs by SOC, preferred term, and maximum severity
- TE AESIs by SOC, preferred term, and maximum severity if applicable
- TE AESIs (regarded as at least possibly related to study drug) by SOC, preferred term, and maximum severity

5.2.2 Clinical Laboratory Tests

Some laboratory parameters will be collected by central and local laboratories. In the cases where a visit's sample is collected on both central and local labs, the central lab result will be presented in the TLF.

Laboratory values outside the reference range will be identified in listings, using flags to identify whether above or below the range limits. Chemistry, Hematology, Coagulation, Urinalysis, and Cytometry results will be presented separately. Laboratory parameters used for pharmacokinetic and pharmacodynamic purposes will be presented separately (see Section 5.3 below).

Listings of all lab results and out of range lab results with their corresponding changes from baseline will be presented. Baseline will be considered as the pre-dose measure on Study Day 1, or the screening assessment if missing the Study Day 1 assessment.

A table of descriptive statistics will be presented for chemistry, hematology, coagulation, urinalysis, and cytometry laboratory results by randomized dose level and by cohort. The number and percent of

subjects with low, normal, and high assessments at each scheduled visit will be tabulated by randomized dose level and by cohort.

5.2.3 *Vital Signs*

The listing of vital sign data will include change from baselines. Baseline will be considered the Study Day 1 pre-dose assessment, or the screening assessment if missing the Study Day 1 assessment. In the listing, data fulfilling the following criteria will be flagged:

Value	Parameter	Low	High
Observed	Systolic Blood Pressure (mmHg)	≤ 80	≥165
	Diastolic Blood Pressure (mmHg)	≤ 40	≥ 95
	Pulse (bpm)	≤ 40	≥120
	Temperature (°C)		≥ 38

*mmHg=millimeters of mercury, bpm=beats per minute, °C=degrees Celsius

A table of descriptive statistics will be presented for each vital sign parameter by randomized dose level and by cohort. The number and percent of subjects with low, normal, and high assessments at each scheduled visit will be tabulated by randomized dose level and by cohort.

5.2.4 *Electrocardiogram (ECG)*

The listing of ECG data will include change from baselines. Baseline will be considered the Study Day 1 pre-dose assessment, or the screening assessment if missing the Study Day 1 assessment.

ECG results will have an overall interpretation and will be classified as normal or abnormal, with the abnormal further classified as either not clinically significant (NCS) or clinically significant (CS). Abnormalities will be documented by the investigator in the eCRF. This information will be included in listings.

Further, in the listing, data fulfilling the following criteria will be flagged:

Value	Parameter	Low	High
Observed	QT, Bazett's QT Correction (QTcB), Fridericia's QT Correction (QTcF) (msec)		≥450
	PR (msec)	≤100	≥240
	QRS (msec)		≥140
	Heart Rate (bpm)	≤40	≥120
Increase from baseline	QT, QTcB, QTcF (msec)		≥30

*msec=milliseconds

A table of descriptive statistics will be presented for each ECG parameter by randomized dose level and by cohort. The number and percent of subjects with low, normal, and high assessments and change from baseline at each scheduled visit will be tabulated by randomized dose level and by cohort.

5.2.5 Physical Examination

Physical examination data will be summarized in listing(s).

5.3 Exploratory Efficacy and Pharmacodynamic Analyses

While the primary objective of this study is safety, exploratory efficacy and pharmacodynamic analyses will be presented. All efficacy analyses will be evaluated on the Intent-to-Treat Set and Per Protocol Set. All pharmacodynamic analyses will be evaluated on the PD Set and Per Protocol Set.

5.3.1 Red Blood Cell (RBC) Transfusions

The absolute and change in number of RBC transfusions per month will be tabulated using descriptive statistics by randomized dose group, by cohort, by phase of the study (Baseline, Part A Core Study Phase and Part B Long Term Extension Phase) and over the whole on-treatment study parts (Part A and Part B combined).

Summary statistics will be presented by study phase as follows:

- Baseline:
  - Number of Transfusions and Units per month for the *n* subjects who had at least 1 infusion in the 365 days prior to first study dose
  - Number of Transfusions and Units per month for the *N* subjects in the dose group (i.e. all subjects in the dose group, regardless of receiving transfusions prior to enrollment)
- Post-Baseline Study Phases (Part A, Part B, Part A and B combined):
  - Number of Transfusions and Units per month for the *n* subjects who had at least 1 infusion in the respective phase
  - Number of Transfusions and Units per month for the *N* subjects in the dose group (i.e. all subjects in the dose group, regardless of receiving transfusions during the respective phase)
  - Change from Baseline of the Number of Transfusions and Units for the N subjects in the dose group (i.e. all subjects in the dose group, regardless of receiving transfusions during the respective phase)

Only whole blood and Packed Red Blood Cell (PRBC) transfusions will be included.

The number of RBC transfusions per month will be calculated for each part of the study as:

$$RBC\ transfusions\ per\ month = \frac{number\ of\ transfusion\ reported\ during\ study\ part\ *\ 28}{number\ of\ days\ in\ that\ part\ of\ study}$$

The whole on-treatment study will be from first dose to last dose received. A similar calculation will be used for the number of units transfused per month.

The baseline number of transfusions per month will be calculated as number of transfusions reported on 12-month transfusion history /12.

All 12-month transfusion history and on study transfusion data will be listed by Cohort. A separate listing of the number of transfusions per month and number of units transfused per month for baseline, each part and over the whole on-treatment study parts will also be included.

5.3.2 Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale

The FACIT Fatigue Scale (Version 4) is an exploratory efficacy endpoint. The individual fatigue score will be calculated as 0-52 (see Section 17.1 of the protocol), where a higher score corresponds to a higher quality of life.

Individual fatigue scores will be listed along with changes from baseline for the ITT Set at each scheduled visit. Study Day 1 will be considered the baseline for the FACIT assessment. If this is missing, change from baseline will not be calculated.

The fatigue score, changes from baseline, and percent changes from baseline will be summarized, using descriptive statistics (mean, SD, median, minimum, and maximum), by randomized dose group and by

cohort at each scheduled study visit for both Part A and Part B of the study.

All individual fatigue scores will be plotted by actual study day, where each subject will be identifiable. The mean score ± SE for each scheduled visit by dose group and cohort will also be plotted. Individual scores and mean changes from baseline ± SE will also be plotted similarly.

The FACIT and all related works are owned and copyrighted by, and the intellectual property of PPD Ph.D. Permission for use of the FACIT-FATIGUE questionnaire is obtained by contacting PPD at information@facit.org.

5.3.3 Linear Analog Self-Assessment (LASA)

The LASA, which consists of five single statements asking respondents to rate, on zero to ten scales, their perceived level of functioning (see Protocol Section 17.2).

Specific domains include physical well-being (i.e., fatigue, activity level), emotional well-being (i.e., depression, anxiety, stress), spiritual well-being (i.e., sense of meaning), and intellectual well-being (i.e., ability to think clearly, concentrate). An item for overall quality of life (QoL) is also included. The Likert scales run from 0 (as bad as it can be) to 10 (as good as it can be), where higher ratings suggest higher QoL.

Individual domain scores and the overall QoL domain score will be listed along with changes from baseline for the ITT Set. Study Day 1 will be considered the baseline for the LASA assessments. If this is missing, change from baseline will not be calculated.

The scores, changes from baseline, and percent changes from baseline for the five domains will be summarized, using descriptive statistics, by

randomized dose group, by cohort, and overall at each scheduled study visit for both Parts A and B of the study.

All individual LASA scores will be plotted by actual study day, where each subject will be identifiable. The mean score ± SE for each scheduled visit by dose group and cohort will also be plotted. Individual and mean changes from baseline ± SE will also be plotted similarly.

5.3.4 Efficacy Laboratory Parameters

Efficacy laboratory parameters include the following:

1. Hemoglobin
2. Lactate Dehydrogenase
3. Reticulocytes
4. Haptoglobin
5. Indirect Bilirubin

Individual data will be listed by along with changes from baseline and percent changes from baseline.

Results, changes from baseline, and percentage changes from baseline will be summarized, using descriptive statistics, at each scheduled study visit by randomized dose group and cohort, in addition to overall.

All individual results will be plotted by actual study day, where each subject will be identifiable. The mean results ± SE for each scheduled visit by dose group and cohort will also be plotted. Individual and mean changes from baseline ± SE will also be plotted similarly.

5.3.5 Pharmacodynamics

PD parameters include the following:

1. Complement CH50
2. Complement AH50
3. Complement C3

Individual data will be listed by along with changes from baseline and percent changes from baseline.

Results, changes from baseline, and percentage changes from baseline will be summarized, using descriptive statistics, at each scheduled study visit by randomized dose group and cohort, in addition to overall.

All individual results will be plotted by actual study day, where each subject will be identifiable. The mean results ± SE for each scheduled visit by dose group and cohort will also be plotted. Individual and mean changes from baseline ± SE will also be plotted similarly.

Additional PD parameters also include the following:

- C3 deposition on RBCs
  - Percent Type I
  - Percent Type II
  - Percent Type III
  - Percent Type I+II
  - Percent C3d on RBC

where:

$$\%C3d\ on\ (Type\ I + II\ RBCs) = \frac{\begin{pmatrix} C3d\ Type\ I\ RBC\ \% * C3d\ Type\ I\ RBC\ Events\ + \\ Type\ II\ RBC\ \% *\ C3d\ Type\ II\ RBC\ Events \end{pmatrix}}{C3d\ Type\ I\ RBC\ Events +\ C3d\ Type\ II\ RBC\ Events}\ x\ 100$$

and where:

$$\%\ C3d\ on\ RBC\ = \frac{C3d + Gly\ RBC\ Events}{Gly + RBC\ Events}\ x\ 100$$

Results, changes from baseline, and percentage changes from baseline will be summarized for each parameter, using descriptive statistics, at each scheduled study visit by randomized dose group and cohort, as well as overall.

A plot of the mean percentage distribution (Type I, Type II, and Type III) ± SE will be plotted by dose group and cohort at each scheduled visit. A different line will specify Type I, Type II, and Type III for each dose group and cohort.

The following will also be plotted at each scheduled visit:

- Percent Type I + II ± SE
- Percent Type I ± SE
- Percent Type II ± SE

All individual results will be plotted by actual study day, where each subject will be identifiable. The mean results ± SE for each scheduled visit by dose group and cohort will also be plotted. Individual and mean changes from baseline ± SE will also be plotted similarly.

5.3.6 Anti-drug antibody Assay

This data will be summarized in listing(s).

5.4 Pharmacokinetic Analysis

All summaries and analyses of the pharmacokinetic data will be based on the Pharmacokinetic Set.

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. For the computation of descriptive statistics, BLQ will be taken as zero, except for the calculation of the geometric mean where the LLOQ will be used.

A listing of all APL-2 concentrations will be presented by dose. The actual study time will be listed, along with the deviation and percent deviation from nominal time.

APL-2 concentrations will be summarized by planned study visit using descriptive statistics by randomized dose group, actual dose at the time of the visit. That is, at each visit, the descriptive statistics will be presented for:

- All randomized 270mg dose group, regardless of current dose
- All randomized 360mg dose group, regardless of current dose
- Subjects randomized to 270mg and on 270mg dose at time of visit
- Subjects randomized to 360mg and on 360mg dose at time of visit

If a subject discontinues APL-2 dosing, then concentrations from samples collected more than 1 day after the last dose will be excluded from calculations.

The number of subjects with a value > BLQ will also be tabulated.

Linear and log-linear (± SE) concentration profile plots against time will be produced for each dose group.

Subjects that changed doses at any point during the study will have individual APL-2 concentration plots against time presented by study day, with APL-2 dose by study day visible on the upper portion of the plot.

PK Parameters

Upon soft-lock of the database, the ADaM Data Structure for Pharmacokinetic Concentrations Analysis (ADPC) set, or other data as requested, will be provided by DPC to the PK analyst. DPC and the PK analyst will ensure that the PK data provided is sufficient for performing non-compartmental analysis (NCA) of PK parameters. Upon completion of the PK analysis, the PK analyst will provide DPC with the PK parameter results. DPC will generate the Study Data Tabulation Model (SDTM) PP domain and the ADaM Data Structure for Pharmacokinetic Parameters Analysis (ADPP) set based on these results.

For each of Part A, Part B, and total time on study, the following PK parameter for APL-2 will be derived using actual sample times:

$C_{trough,max}$	Maximum observed serum concentration. As later PK samples are collected pre-dose this is termed maximal trough concentration.

$C_{trough,max}$ will be calculated for both 270 mg and 360 mg where subjects receive both doses during Part A.

PK parameters will be listed by cohort and dose (for $C_{trough,max}$). PK parameters will also be summarized using descriptive statistics. Geometric mean and CV will be included in the descriptive statistics. Additional NCA analyses and additional analyses may be performed and summarized as deemed necessary upon review of the data.

Population PK and PD Modelling

In addition to the above analyses, all PK and complement C3 serum concentration data may be used to develop the population PK and exposure-response models in conjunction with other clinical study data. The methods and procedures will be described in a separate Analysis Plan if needed.

6. TESTING/QUALITY CONTROL PLAN AND SOFTWARE/SYSTEM

All statistical programs, excluding PK analysis programs, will be written in SAS® version 9.4. Statistical programs will be tested and reviewed for Quality Control (QC) by a second programmer/biostatistician not involved in the programming as per DPC's standard operating procedure (SOP). In addition, DPC's SOP will be followed to ensure that the information is complete, consistent, and accurately reflects the data stored in the database. Further all TLFs will undergo a QC process by an independent biostatistician/programmer to ensure that the information is complete, consistent, and accurately reflects the data.

The PK analysis will be performed using PKNCA version 0.8.51 or higher with R version 3.2.32 or higher.

6.1 Programming Specifications for TLFs

Appendix 8.1 provides a list of all the TLFs that are planned to be produced.

6.2 Formatting Conventions

The following formatting conventions will be used to output TLFs:

- TLFs are outputted by SAS Output Delivery System (ODS) into Rich Text Files (RTF) format.
- Tables and Listings will include borders around all headings and data cells.
- Output will be in landscape orientation with margins of 0.5 inches on top, right, and left, and 1 inch for bottom.
- The default font to be in tables/listings/figures will be Courier New.
- Preferred and minimum font size:

Portion of Output	Preferred	Minimum
Page Header	9 pt	8 pt
Title	9 pt	8 pt
Column header	9 pt	8 pt
Cells	9 pt	8 pt
Footnote	9 pt	8 pt

Page Footer	9 pt	8 pt

- Data will be centered within columns when the maximum length of the data being displayed is less than or equal to the maximum width of the column heading. When the maximum length of the data being displayed exceeds the maximum width of the column heading, the data will be left-justified.
- Column headings should be in initial capital characters. For numeric variables, include "unit" in the column heading when appropriate.
- In figures, axes will be labeled appropriately.

6.3 Standard Text Conventions

6.3.1 Header

All output (table, listing, or figure) will have the following header, as applicable:

```
Apellis Pharmaceuticals, Inc.
Protocol: APL2-CP-AIHA-208                                  Page xx of XX
[Part A Study Report]/[Clinical Study Report]
```

All output will have the date and time (date and time output was generated) and internal page number in the header. Tables/Listings/Figures should be internally paginated (i.e., page numbers should appear sequentially within each output).

6.3.2 Title

At least three (3) lines, in general, will be reserved for the entire title.

- The first line is for the table/listing/figure number;
- The second line is for the actual title; and
- The third line is reserved for the analysis set descriptor.

All titles will be centered, as shown in the following example:

```
                                  Table 14.3.1.1
```

Topline Summary of Adverse Events
Safety Set

6.3.3 *Footnotes*

Unless otherwise specified, footnotes will appear on all pages within the tables and listings as follows:

- Footnotes will be in the format of "NOTE: followed by 2 spaces, then the footnotes", as shown in the following example:

```
NOTE:  SD = Standard Deviation.
```

- Each line of a complete footnote should end with a period.
- When an abbreviation (e.g. AE, SAE, etc.) appears first time in the whole set of TLFs for a study, a footnote should be provided at least once; and it is up to the study statistician, to decide whether there is a need to repeat the same footnote for the rest of TLFs.
- A footnote serves as a brief explanation/clarification /definition /concept of a flag symbol or a character, an abbreviation, a terminology, etc., that appears in or relates directly to the displayed content of a table/listing/figure.
- All footnotes will be at the lowest line of the page immediately above the footer. The footer will be directly on the line below the last footnote.
- For Tables, first footnote will provide source listings and/or analysis datasets names for cross-referencing.

6.3.4 *Footer*

The following footer should appear at the very bottom of each page of a table, a listing, or a figure generated in SAS in the lower left corner:

```
Program Name: PGNAME.sas; Creation Date and Time: DDMMMYYYY HH:MM
Data Cutoff DDMMMYYYY HH:MM - ADaM Generated DDMMMYYYY Proprietary and Confidential
```

where PGNAME = SAS program name.

6.4 Statistical Conventions

6.4.1 Statistics Reported

- Unless otherwise specified, the mean and SD will be displayed to one more decimal place than the original value, while minimum and maximum will be reported in the format of the original data, e.g.:

  Original: xx

  Mean and SD: xx.x

  Minimum and maximum: xx

- Use of N versus n:

  N = total number of subjects or subjects in the analysis set.

  n = total number of subjects or subjects in the specific category.

- Descriptive statistics in this template include: N. Mean, Median, SD, Minimum, and Maximum.
- Unless specified in the actual TLF shells for a study, all percentages will be rounded to 1 decimal place in all tables/listings/figures. Rounding will take place after all calculations have been performed.

6.4.2 Tables Summarizing Categorical Data

The following specifications apply to tables that summarize categorical data:

- If the categories of a parameter are ordered, then all categories between the maximum possible category and the minimum category will be included, even if n=0 for a given category between the minimum and maximum level for that parameter.
- If the categories are not ordered, then only those categories for which there is at least one subject represented will be included.
- A missing category will be added to any parameter for which information is not available for any subjects.

6.4.3 Subject Data Listings

In general, individual subject data listings will include the data of all non-screen failure subjects. However, if a subject data listing includes

only subjects who met a certain condition, and there were no subjects who met that condition, then a "message" will appear indicating that no subjects met the condition for inclusion in that listing. Data listings will provide the derived study day of an assessment or event, where appropriate.

7. REFERENCES

ICH E3 (1995): Structure and Content of Clinical Study Reports. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

ICH E6 R2 (2016): Integrated Addendum to ICH E6(R1). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

ICH E9 (1998): Statistical Principles for Clinical Trials. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

MedDRA Version 20.0 (March 2017). International Federation of Pharmaceutical Manufacturers and Associations (IFPMA).

Novel Insights into the treatment of complement-medicated hemolytic anemia. Berentsen S et al, (2019). Therapeutic Advances in Hematology. Vol 10: 1-20.

Population Pharmacokinetic Analysis Plan for APL-2 Phase 1 Data (August 2015). Apellis Pharmaceuticals, Inc.

R: A language and environment for statistical computing (2012). R Core Team, R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/.

SAS® for Windows® Version 9.4. SAS Inc. Cary, North Carolina USA.

Simple, Automatic Noncompartmental Analysis: The PKNCA R Package. Denney W, Duvvuri S and Buckeridge C (2015). Journal of Pharmacokinetics and Pharmacodynamics, 42(1), pp. 11-107,S65. ISSN 1573-8744, doi: 10.1007/s10928-015-9432-2

The WHO Drug Dictionary (WHO-DD) (March 2017). World Health Organization (WHO) Uppsala Monitoring Center (UMC).

Certificate Of Completion

Envelope Id: CCI [redacted]
Status: Completed
Subject: Please DocuSign: APL2-CP-AIHA-208 Statistical Analysis Plan v1.0 2020-04-27.pdf
Source Envelope:
Document Pages: 57
Signatures: 4
Envelope Originator:
Certificate Pages: 5
Initials: 0
PPD
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC-05:00) Eastern Time (US & Canada)

Record Tracking

Status: Original
4/27/2020 6:46:17 PM
Holder: PPD
Location: DocuSign

Signer Events	Signature	Timestamp
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 4/27/2020 6:55:37 PM Viewed: 4/27/2020 6:56:38 PM Signed: 4/27/2020 6:57:31 PM
Electronic Record and Signature Disclosure: Accepted: 4/27/2020 6:56:38 PM ID: PPD		
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 4/27/2020 6:57:35 PM Viewed: 4/28/2020 8:37:37 AM Signed: 4/28/2020 8:38:14 AM
Electronic Record and Signature Disclosure: Accepted: 4/28/2020 8:37:37 AM ID: PPD		

Signer Events	Signature	Timestamp
PPD Apellis Pharmaceuticals, Inc. Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 4/28/2020 8:38:19 AM Resent: 4/28/2020 4:19:04 PM Viewed: 4/28/2020 4:15:58 PM Signed: 4/28/2020 4:44:40 PM
Electronic Record and Signature Disclosure: Accepted: 10/31/2019 11:45:03 AM ID: PPD		
PPD PPD Biostatistics PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 4/28/2020 4:44:46 PM Viewed: 4/28/2020 4:46:48 PM Signed: 4/28/2020 4:47:12 PM
Electronic Record and Signature Disclosure: Accepted: 1/20/2020 9:39:44 PM ID: PPD		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	4/28/2020 4:44:46 PM
Certified Delivered	Security Checked	4/28/2020 4:46:48 PM
Signing Complete	Security Checked	4/28/2020 4:47:12 PM
Completed	Security Checked	4/28/2020 4:47:12 PM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

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ii. send us an e-mail to PPD and in the body of such request you must state your e-mail, full name, IS Postal Address, telephone number, and account number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

Operating Systems:	Windows2000? or WindowsXP?
Browsers (for SENDERS):	Internet Explorer 6.0? or above
Browsers (for SIGNERS):	Internet Explorer 6.0?, Mozilla FireFox 1.0, NetScape 7.2 (or above)
Email:	Access to a valid email account
Screen Resolution:	800 x 600 minimum
Enabled Security Settings:	• Allow per session cookies

	• Users accessing the internet behind a Proxy Server must enable HTTP 1.1 settings via proxy connection

** These minimum requirements are subject to change. If these requirements change, we will provide you with an email message at the email address we have on file for you at that time providing you with the revised hardware and software requirements, at which time you will have the right to withdraw your consent.

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Part B Long Term Extension Statistical Analysis Plan

Study Title:	An Open Label, Prospective, Study to Assess the Safety, Tolerability, Efficacy and Pharmacokinetics of APL-2 in Patients with Warm Antibody Autoimmune Hemolytic Anemia (wAIHA) or Cold Agglutinin Disease (CAD)
Protocol Number:	APL2-CP-AIHA-208
Amendment	Version 1.0 Amendment 4.0 / 17 Jan 2019
Sponsor:	Apellis Pharmaceuticals, Inc. 100 5th Avenue, 3rd Floor Waltham, MA 02451
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Version No./Date	Version 1.0 / 08 Nov 2022

Signatory Page

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08-Nov-2022

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Date

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Approval

PPD

PPD

Biostatistician (Contract)

Apellis Pharmaceuticals, Inc.

Approval

PPD

PPD

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Apellis Pharmaceuticals, Inc.

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Approval 08-Nov-2022

PPD Date

Apellis Pharmaceuticals, Inc.

REVISION HISTORY

Version No.	Version Date	Description of Modifications
1.0	08 Nov 2022	Original Document

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS AND ACRONYMS

Abbreviations and Acronyms	Description
°C	Degrees Celsius
ADaM	Analysis Data Model
ADDV	ADaM Data Structure for Protocol Deviation Analysis
ADPC	ADaM Data Structure for Pharmacokinetic Concentrations Analysis
ADPP	ADaM Data Structure for Pharmacokinetic Parameters Analysis
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIHA	Autoimmune Hemolytic Anemia
ATC	Anatomical Therapeutic Chemical
CAD	Cold Agglutinin Disease
BLQ	Below the Limit of Quantification
bpm	beats per minute
CFB	Change From Baseline
$C_{trough, max}$	Maximal Trough Concentration
CS	Clinically Significant Abnormality
DPC	DP Clinical Inc.
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ET	Early Termination
ETFU	Early Termination Follow-up
FACIT	Functional Assessment of Chronic Illness Therapy
HiB	Haemophilus Influenzae Type B
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ITT	Intent-to-Treat
LASA	Linear Analog Scale Assessment
LDH	Lactate Dehydrogenase

Abbreviations and Acronyms	Description
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeters of Mercury
msec	Milliseconds
NCS	Not Clinically Significant
ODS	Output Delivery System
QC	Quality Control
QoL	Quality of Life
PRBC	Packed Red Blood Cell
PCFB	Percent Change From Baseline
PCS	Potentially Clinically Significant
PCV13	Pneumococcal Conjugate Vaccine
PD	Pharmacodynamics
PI	Principal Investigator or Designee
PK	Pharmacokinetics
PP	Per Protocol
PPSV23	Pneumococcal Polysaccharide Vaccine 23
PT	Preferred Term
RBC	Red Blood Cell
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
TLFs	Tables, Listings and Figures
wAIHA	Warm Antibody Autoimmune Hemolytic Anemia
WHO	World Health Organization

Abbreviations and Acronyms	Description
WHODrug	World Health Organization Drug Dictionary
WOCBP	Woman of Childbearing Potential

2. INTRODUCTION

This Statistical Analysis Plan (SAP) is prepared to provide a more technical and detailed elaboration of the principal statistical features stated in the protocol. The SAP will ensure that the tables, listings, and figures that will be produced and statistical methods that will be used for the final analysis are complete and accurate and will allow valid conclusions to be drawn.

In the development of this final analysis SAP, the following study documents were used:

- Protocol Number (Version 1.0 Amendment 4), 17 Jan 2019
- Electronic Case Report Form (eCRF), extracted 18 Oct 2021
- Medical Coding Guidelines (Version 5.0), 10 Sep 2021

The study protocol consists of two study parts for analysis (details of the scheduled assessments of the study parts can be found in Section 3.3 of the SAP):

- Core Study Phase (Part A): the study period of the daily 270/280 mg or 360 mg APL-2 dose regimen.
- Long Term Extension Phase (Part B): the study period of the twice or three times weekly 1080 mg APL-2 dose regimen.

Statistical Analysis Plan Version 1.0 was used for the production of the Interim Part A Core Study Phase Analysis. This SAP will present the results for the final analysis for subjects who rolled over into Part B, presenting the safety and efficacy results of Part B and Part A + B as whole completed study as well. Definitions for the study days and baselines are outlined in Section 4. Details of the planned analyses are outlined in Section 5.

In the event that a discrepancy is found between the descriptions in the statistical section of the protocol and this document, the description in this document supersedes the descriptions in the statistical section of the protocol. Any deviations from the final analysis plan or from what is outlined in the protocol will be discussed in the final study report.

3. STUDY OVERVIEW

This study is being conducted as part of a series of studies for the clinical development of APL-2. This study will be the initial exploration of APL-2 in patients with a primary diagnosis of Warm Antibody Autoimmune Hemolytic Anemia (wAIHA) who relapsed from, did not respond to, or did not tolerate at least one prior wAIHA treatment regimen (such as prednisone, rituximab, or splenectomy), or a primary diagnosis of Cold Agglutinin Disease (CAD) regardless of prior treatment history.

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 a primary diagnosis of wAIHA who relapsed from, did not respond to, or did not tolerate at least one prior wAIHA treatment regimen (such as prednisone, rituximab, or splenectomy), or a primary diagnosis of CAD regardless of prior treatment history.

An exploratory objective of the study is to assess the pharmacodynamics (PD) of multiple SC doses of APL-2 when administered to wAIHA and CAD patients.

3.2 Study Endpoints

3.2.1 Primary Safety Endpoint

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

3.2.2 Efficacy Endpoints

- Change from baseline in hemoglobin
- Number of red blood cell (RBC) transfusions during the study
- Change from baseline in absolute reticulocyte count
- Change from baseline in lactate dehydrogenase (LDH)
- Change from baseline in haptoglobin
- Change from baseline in indirect bilirubin

- APL-2 serum concentrations and PK parameters, as appropriate
- Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT) scale and the Linear Analog Scale Assessment scale (LASA) including energy level, ability to perform daily activity, and overall quality of life (QoL)

3.2.3 Exploratory Study Endpoints

Exploratory PD markers include:

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

3.3 Study Design

This is a Phase II, open-label, prospective pilot study of APL-2 conducted in subjects with a primary diagnosis of wAIHA or CAD in parallel. The study will consist of up to 24 subjects, a target of 12 subjects with a primary diagnosis of wAIHA in Cohort 1 and a target of 12 subjects with a primary diagnosis of CAD in Cohort 2. Subjects will be randomized 1:1 to a 270mg or 360mg daily SC APL-2 dosage group within each cohort for up to 12 months (Part A, the Core Study Phase).

Following Day 336 and the completion of the Part A Core Study Phase, subjects will be eligible to participate in Part B, a Long-Term Extension Phase, in order to continue to receive treatment with APL-2. The Long-Term Extension Phase is described later in this section.

Through Part A (Day 336), dose escalation from 270 mg/d to 360 mg/d, or de-escalation from 360 mg/day to 270 mg/day may occur after a thorough evaluation of available safety and laboratory assessment.

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.

Part A: Core Study Phase:

Screening will take place within 30 days prior to the start of dosing on Day 1. If needed (see inclusion criteria), *Neisseria meningitides* types A, C, W, Y and B (administered as two separate vaccines), Pneumococcal Conjugate Vaccine (PCV13) or Pneumococcal Polysaccharide Vaccine 23 (PPSV23), and Haemophilus Influenzae Type B (Hib) vaccinations will be administered prior to dosing on Day 1.

Subjects who meet all the inclusion criteria and none of the exclusion criteria will be enrolled into the study on Day 1 at a time designated by the Principal Investigator or designee (PI). During study, the first 3 daily SC doses of APL-2 (Day 1 to 3) as well as doses on Day 7 and Day 14 will be administered at the clinical site. From Day 4 to Day 336 daily doses of APL-2 will be administered off-site by a study nurse or self-administered by the subject and/or caregiver, at the subject's home, workplace, or other location convenient to the subject with the exception of those days where dosing is at the clinical site. At any time during the study, if subjects discontinue treatment, or if after the conclusion of the Part A Core Study Phase a subject does not elect to enter the Part B Long-Term Extension Phase, subjects will return to the clinical site for safety follow-up study procedures after 6 weeks, followed by final study procedures at an Exit Visit after another 6 weeks. See Study Flowchart in Section 3.3.2.

The planned length of participation in the study for each subject is at least approximately 450 days (from Day –30 through completion of the Day 420 Exit visit procedures [for subjects that do not elect to enter the Part B Long-Term Extension Phase]). Subjects that continue in the Part B Long-Term Extension Phase may continue to receive treatment indefinitely until the subject discontinues or the development program is terminated. The study duration may change in the event that the study is terminated early, additional subjects are needed, additional time is required to review safety between groups, or extended safety and PK sampling is added for a dose group (e.g. beyond Day 420).

Part B: Long-Term Extension Phase:

Following Visit 15 (Week 48), subjects who elect to continue in the Part B Long-Term Extension Phase will return to the site at 12-week intervals indefinitely until the subject discontinues or the development program is terminated.

Specific procedures for each visit are listed in the Study Flow Chart for the Long-Term Extension Phase in Table 2 in Section 3.3.2.

At Visit 15 (Week 48), subjects electing to enter the Part B Long-Term Extension Phase will begin an APL-2 dose regimen of APL-2 1,080 mg twice weekly (with potential to escalate to APL-2 1,080 mg every 3 days). When switching from the Part A Core Study Phase formulation and dose of APL-2 (270 mg/d or 360 mg/d) to the formulation and dose intended for use in the Long-Term Extension Phase (APL-2 1,080 mg twice weekly), subjects should return to the site for APL-2 administration training and to conduct Dose Transition Visits 1, 2 and 4 weeks after the new dose is initiated and perform the procedures outlined in Appendix Section 8.1.

Subjects who plan on continuing in the Part B Long-Term Extension Phase should be instructed to skip their daily Part A Core Study Phase Dose the day prior to Visit 15 (i.e., the subject should not self-administer APL-2 on Day 335).

Note: The first dose of APL-2 1,080 mg should be administered at the Visit 15 (Day 336), with Dose Transition Visits at Week 49, Week 50, and Week 52. Some subjects may enter the Part B Long-Term Extension Phase prior to the availability of the sorbitol formulation. These subjects should continue on their Part A Core Study Phase dose into the Part B Long-Term Extension Phase. These subjects will transition to the Long-Term Extension Phase dose at the next scheduled visit at which the sorbitol formulation and dose is available, and should schedule Visits T1, T2, and T3 1, 2 and 4 weeks following the visit at which the sorbitol dose is initiated. These subjects should be instructed to skip their Part A dose the day before the visit at which the APL-2 1,080 mg twice weekly dose regimen is scheduled to be initiated.

Subjects who discontinue treatment early should complete one Early Termination Follow-up Visit (ETFU) 6 weeks after discontinuation of treatment, and one Early Termination (ET) Exit Visit 6 weeks after the ETFU as outlined in Appendix 8.1.

Study Assessments that align with those conducted in the Core Study Phase and are described in Section 13 of the Clinical Study Protocol and assessments that align with those conducted in the Long-Term Extension Phase are described in Section 17.3.2 of the Clinical Study Protocol (Version 1.0 Amendment 4), 17 Jan 2019.

3.3.1 Sample Size Considerations

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

3.3.2 Study Assessments Schedules

Study assessments are described in detail in Section 12.0 of the protocol (Version 1.0 Amendment 4) and summarized in Study Flow Charts for Part A and Part B in Appendix Section 8.1.

4. GENERAL CONSIDERATIONS

4.1 Analysis Sets

After all the data have been verified/coded/entered into the database, a review will be performed by DP Clinical, Inc (DPC) and the sponsor. The purpose of this review will be to define the analysis sets. The review will also check the quality of the data, identifying outliers, and making decisions on how to deal with problems in any data (e.g., missing values, withdrawals, protocol deviations). After the pre-analysis review, resolution of all issues and documentation of all decisions, the database will be locked.

All Enrolled Subjects:

All Enrolled Subjects will include all subjects that signed an informed consent during the Screening Period prior to Part A. All Enrolled Subjects will be used only for summaries of disposition from Part A through Part B and the end of study.

Safety Set / Intent-to-Treat (ITT) / Pharmacodynamic (PD) Set:

Safety Set will only include the subjects who roll over to Part B and receive at least one dose of 1080 mg APL-2.

ITT Set and PD Set will be identical to the Safety Set for this study.

Per Protocol (PP) Set:

PP Set will only include subjects who were in the PP set in Part A and roll over to Part B and have not violated any inclusion or exclusion criteria and/or deviated from the protocol in a way that could influence their efficacy assessment while on study in Part B.

The PP Set will be used in efficacy analyses for Part B and Part A + B.

Decisions concerning the exclusion of subjects from the PP sets will be made and documented during an adjudication by DPC and the sponsor prior to database lock.

Pharmacokinetic (PK) Set:

The PK Set will only include all subjects in the Safety Set who rolled over into Part B and have at least one evaluable non-BLQ post-dose PK measurement.

4.2 Definitions

4.2.1 Study Day

Part A + B:

Study Day 1 for Part A + B will be the day a subject takes the first dose of APL-2, which will be calculated as:

For events that occurred on the day of or after administration of the first APL-2 dose:

Part A + B Study Day = visit date – date of first APL-2 dose + 1

For events that occurred on days before administration of the first APL-2 dose:

Part A + B Study Day = visit date – date of first APL-2 dose

Part B:

Part B is considered all visits and assessments from the date of first 1080 mg APL-2 dose through the date of last APL-2 dose.

For events that occurred on the day of or after administration of the first 1080 mg APL-2 dose in Part B Long Term Extension Phase:

Part B Study Day = visit date – date of first 1080 mg APL-2 dose + 1

For events that occurred on days before administration of the first 1080 mg APL-2 dose:

Part B Study Day = visit date – date of first 1080 mg APL-2 dose

4.2.2 Baseline and Change from Baseline

Summary tables will present: 1) change from Part A baseline summaries assessments during Part A + B and 2) change from Part B baseline

summaries assessments during Part B. This section outlines the definitions for baseline and change from baseline for all safety and efficacy assessments collected during study visits, except for transfusions (see Section 5.3.1).

Part A + B

The baseline for Part A + B summaries will be the Part A Baseline. Unless indicated otherwise Change from Part A+ B Baseline (Part A + B CFB) will be calculated as follows:

Part A + B CFB = Visit Result – Part A Baseline Result

Percent Change from Part A + B Baseline (Part A + B PCFB) will be calculated as follows:

Part A + B PCFB (%) = 100(Visit Result – Part A Baseline Result)/ (Part A Baseline Result),*

where Part A baseline is the last assessment prior to the first APL-2 dose in Part A.

Part B

Part B baseline for this study will be derived as the last measure prior to the first 1080 mg APL-2 dose.

Unless indicated otherwise Part B change from baseline (Part B CFB) will be calculated as follows for after Part B Study Day 1:

Part B CFB = Visit Result – Part B Baseline Result

Percent change from baseline (Part B PCFB) will be calculated as follows:

Part B PCFB (%) = 100(Visit Result – Part B Baseline Result)/ (Part B Baseline Result)*

Where Part B Baseline is the last assessment prior to the first 1080 mg APL-2 dose on Part B Study Day 1.

4.2.3 Visit Windowing Based on Study Day

Data will be summarized and analyzed based on the list of visits specified in table below for Part A + B and the Part B. The relative day will be used to assign analysis visit following the table below. All the records post-baseline will be assigned to an appropriate analysis visit using the following:

For the post-baseline visits, the lower and the upper bound for the analysis visit windows are defined as the midpoints of the target date of the scheduled visits. If the date of assessment falls in between the lower bound and the upper bound for a visit as specified in the schedule of assessments of the protocol, then it will be assigned to that visit. If the interval separating 2 scheduled visits is an even number of days, the middle day will be included in the lower bound of the next visit. If more than 1 record is within the same analysis visit window, the record closest to the midpoint of the interval will be used in the analysis. If 2 records are tied before and after the middle of the interval, the earlier record will be used in the analysis. 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.

In listings that are presented by visit, windowed assessments that are used in the analysis tables by visit will be identified.

Table 1: Visit Windowing for Part A + B Analyses

Part	Study Visit	Target Day	Analysis Window	Interval
Part A + B	Part A Visit 1 (Screening)	Part A+B Study Day -30	<1*	NA
	Part A Visit 2 (Baseline)	Part A+B Study Day 1	1*	1
	Part A Visit 3 (Day 2)	Part A+B Study Day 2	2	1
	Part A Visit 4 (Day 3)	Part A+B Study Day 3	3	1
	Part A Visit 5 (Day 7)	Part A+B Study Day 7	>=4- < 11	7

Part A + B, cont.	Part A Visit 6 (Week 2)	Part A+B Study Day 14	11– < 21	10
	Part A Visit 7 (Week 4)	Part A+B Study Day 28	21- < 42	21
	Part A Visit 8 (Week 8)	Part A+B Study Day 56	42 - <70	28
	Part A Visit 9 (Week 12)	Part A+B Study Day 84	70 - < 98	28
	Part A Visit 10 (Week 16)	Part A+B Study Day 112	98 - < 126	28
	Part A Visit 11 (Week 20)	Part A+B Study Day 140	126 - < 154	28
	Part A Visit 12 (Week 24)	Part A+B Study Day 168	154 - < 196	42
	Part A Visit 13 (Week 32)	Part A+B Study Day 224	196 - < 252	56
	Part A Visit 14 (Week 40)	Part A+B Study Day 280	252 - < 308	56
	Part A Visit 15 (Week 48)	Part A+B Study Day 336	308 - < 378	70
	Part A Visit 16 (Week 60)	Part A+B Study Day 420	378 - < 462	84
	Part A Visit 17 (Week 72)	Part A+B Study Day 504	462 - < 546	84
	Subjects who had assessments at Part A Visit 16/17 are included in safety summaries but not efficacy summaries.			
	Part B Baseline (Day 1)	Date of First 1080 mg Dose = Part B Study Day 1	≤ Part B Study Day 1*	NA
	Part B Transition Visit 1 (Day 7)	Part B Study Day 7	> Part B Study Day 3 - < Part B Study Day 11	7
	Part B Transition Visit 2 (Week 2)	Part B Study Day 14	Part B Study Day 11 - < Part B Study Day 21	10
	Part B Transition Visit 3 (Week 4)	Part B Study Day 28	Part B Study Day 21 - < Part B Study Day 56	25
	Part B Visit 1 (Week 12)	Part B Study Day 84	Part B Study Day 56 - Part B Study Day < 126	70
	Part B Visit 2 (Week 24)	Part B Study Day 168	Part B Study Day 126 - Part B Study Day < 210	84
	Part B Visit 3 (Week 36)	Part B Study Day 252	Part B Study Day 210 - Part B Study Day < 294	84
	Part B Visit 4 (Week 48)	Part B Study Day 336	Part B Study Day 294 - Part B Study Day < 378	84
	Part B Visit 5 (Week 60)	Part B Study Day 420	Part B Study Day 378 - Part B Study Day < 462	84
	Part B Visit 6 (Week 72)	Part B Study Day 504	Part B Study Day 462 - Part B Study Day < 546	84

Part A + B, cont.	Part B Visit 7 (Week 84)	Part B Study Day 588	Part B Study Day 546 - Part B Study Day < 630	84
	Part B Visit 8 (Week 96)	Part B Study Day 672	Part B Study Day 630 - Part B Study Day < 714	84
	Part B Visit 9 (Week 108)	Part B Study Day 756	Part B Study Day 714 - Part B Study Day < 798	84
	Part B Visit 10 (Week 120)	Part B Study Day 840	Part B Study Day 798 - Part B Study Day < 882	84
	Part B Visit 11 (Week 132)	Part B Study Day 924	Part B Study Day 882 - Part B Study Day < 966	84
	Part B Visit 12 (Week 144)	Part B Study Day 1008	Part B Study Day 996 - Part B Study Day < 1050	84
	Part B Visit 13 (Week 156)	Part B Study Day 1092	Part B Study Day 1050 - Part B Study Day < 1134	84
	Part B Visit 14 (Week 168)	Part B Study Day 1176	Part B Study Day 1134 - Part B Study Day < 1218	84

*For baseline assessments, must be prior to dosing.

Table 2: Visit Windowing For Part B

Part	Study Visit	Target Day	Analysis Window	Interval
Part B	Part B Baseline (Day 1)	Date of First 1080 mg Dose = Part B Study Day 1	≤ Part B Study Day 1*	NA
	Part B Transition Visit 1 (Day 7)	Part B Study Day 7	> Part B Study Day 3 - < Part B Study Day 11	7
	Part B Transition Visit 2 (Week 2)	Part B Study Day 14	Part B Study Day 11 - < Part B Study Day 21	10
	Part B Transition Visit 3 (Week 4)	Part B Study Day 28	Part B Study Day 21 - < Part B Study Day 56	25
	Part B Visit 1 (Week 12)	Part B Study Day 84	Part B Study Day 56 - Part B Study Day < 126	70
	Part B Visit 2 (Week 24)	Part B Study Day 168	Part B Study Day 126 - Part B Study Day < 210	84
	Part B Visit 3 (Week 36)	Part B Study Day 252	Part B Study Day 210 - Part B Study Day < 294	84
	Part B Visit 4 (Week 48)	Part B Study Day 336	Part B Study Day 294 - Part B Study Day < 378	84
	Part B Visit 5 (Week 60)	Part B Study Day 420	Part B Study Day 378 - Part B Study Day < 462	84
	Part B Visit 6 (Week 72)	Part B Study Day 504	Part B Study Day 462 - Part B Study Day < 546	84
	Part B Visit 7 (Week 84)	Part B Study Day 588	Part B Study Day 546 - Part B Study Day < 630	84
	Part B Visit 8 (Week 96)	Part B Study Day 672	Part B Study Day 630 - Part B Study Day < 714	84

Part	Study Visit	Target Day	Analysis Window	Interval
Part B, cont.	Part B Visit 9 (Week 108)	Part B Study Day 756	Part B Study Day 714 - Part B Study Day < 798	84
	Part B Visit 10 (Week 120)	Part B Study Day 840	Part B Study Day 798 - Part B Study Day < 882	84
	Part B Visit 11 (Week 132)	Part B Study Day 924	Part B Study Day 882 - Part B Study Day < 966	84
	Part B Visit 12 (Week 144)	Part B Study Day 1008	Part B Study Day 996 - Part B Study Day < 1050	84
	Part B Visit 13 (Week 156)	Part B Study Day 1092	Part B Study Day 1050 - Part B Study Day < 1134	84
	Part B Visit 14 (Week 168)	Part B Study Day 1176	Part B Study Day 1134 - Part B Study Day < 1218	84

*For baseline assessments, must be prior to dosing.

For the purposes of the all safety and efficacy summary tables and figures by visit, there will be one result per subject per parameter per planned visit per baseline type (Part A + B Baseline and Part B Baseline). The result will be selected in the following priority within each planned subject, visit, parameter, and baseline type:

1) Ensure there is an evaluable result (i.e. do not prioritize a NOT DONE assessment)
2) Select the date closest to the midpoint of the analysis window per the windowing rules in Section 4.2.3
3) For laboratory parameters with central and local labs on the same date, if there is the same date with both local and central lab results, the central lab result is selected

4.3 Test Hypothesis and *P*-Value Justification

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

4.4 Procedures for Handling Missing Data and Dropouts

A missed visit and assessment details eCRF page will summarize which visits / assessments were missed along with the reason (e.g., COVID-19, or other). This will be listed for both Part A + B and Part B.

4.4.1 Safety Data

Where appropriate, screening values may be used as baseline in the event of missing or unusable Day 1 measurements. No imputation of missing data for early terminations will be performed.

However, both partial and completely missing dates/times that are not related to early terminations, in addition to missing safety data (e.g., missing severities) will be reviewed on a case-by-case basis for potential imputations. As a general rule, a conservative approach will be adopted as outlined in Section 5.2.1 (e.g. partial Adverse Event (AE) onset dates and missing severities will be taken as the earliest 'on treatment' start date and highest severity, respectively, consistent with the partial information available). Moreover, the original data, without imputations, will be presented separately in data listings.

For safety lab parameters that are below or above the limit of quantification, the data will be presented as-is in the listings, but the limit of quantification will be used for the purposes of calculating change from baseline.

4.4.2 PK and Efficacy/PD Concentration Data

APL-2 concentrations reported from pre-dose on Day 1 to the time of the first quantifiable value will be taken as zero for linear plots and the calculation of PK parameters, and equal to the lower limit of quantification (LLOQ) for semi-logarithmic plots.

After this time point, concentrations below the limit of quantification (BLQ) will be set to zero, with the exception of the calculation of the geometric mean where the LLOQ will be used.

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

In the event of a missing PD baseline value a screen measurement or pre-dose unscheduled measurement may be used (whichever is closer to the baseline date).

If a baseline PD value is zero, then the percent change from baseline will not be calculated. If a post baseline value is BLQ, then the value will be set to the LLOQ. Similarly, for PD plots, a BLQ value will be set equal to LLOQ.

4.5 Subgroup Analysis

Due to the small sample size of the study, no subgroup analyses will occur.

4.6 Multi-Center Studies and Pooling of Centers

This is a multi-center study. Due to the small number of subjects at each site, no adjustments will be made for study site.

5. STATISTICAL ANALYSIS METHODOLOGY

In general, tables will be presented by cohort (Cohort 1 wAIHA / Cohort 2 CAD) and study part (Part A + B / Part B). The Part B summaries will start from Study Day 1 in Part B through the end of the Part B Long Term Extension Phase, while Part A + B will start from Study Day 1 in Part A through the end of the Part B Long Term Extension Phase.

Tabulations for continuous data will use a standard set of descriptive statistics for the results and for change from baseline, as specified: number of observations available (n), mean, standard deviation (SD), median, and range (minimum, maximum). Change from Baseline for Part A + B summaries will calculate the Change from Part A Baseline summary statistics. Change from Baseline for Part B summaries will calculate the Change from Part B Baseline summary statistics.

Categorical or dichotomous data will be tabulated using frequencies (counts and percentages). The numerator and denominator for each percentage calculation will be specified in the footnotes of table shells. Categorical data will be populated as appropriate for each study part (Part A + B and Part B).

Data listings will present all information recorded in eCRFs for all subjects and visits. All listings will be sorted by cohort and subject number.

5.1 Study Subjects

5.1.1 Subject Disposition

The subject disposition will summarize All Enrolled Subjects from Screening prior to Part A through the end of Part B. The following disposition categories will be tabulated by cohort (Cohort 1 wAIHA / Cohort 2 CAD):

- Number of subjects screened
- Screen Failure Reasons
- Number of subjects who discontinued prior to the first dose of APL-2

- Number of subjects who receive at least at least one dose of APL-2 in Part A phase (Safety Set in Part A Core Study Phase)
- Number of subjects who completed treatment phase through Visit 15
- Number of subjects in the Part A PP Set
- Number of early termination subjects during Part A Core Study Phase with reason for early termination
- Number of subjects who discontinued after Part A completion and prior to Part B with reason for termination
- Number of subjects who receive at least one 1080 mg APL-2 dose in Part B phase (Safety/ITT/PD Set)
- Number of subjects in Per Protocol set per definition in Section 4.2
- Number of subjects in PK set
- Reason for Withdrawal during Part B Long Term Extension Phase

5.1.2 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedure defined in the protocol.

The following categories will be used to group protocol deviations:

1. Eligibility Not Met
2. Study Assessment Noncompliance
3. Study Drug Noncompliance
4. Study Schedule Noncompliance
5. Other

The following are categorical reasons used to document why a protocol deviation occurred:

1. Subject Illness
2. Subject Unable to Comply

3. Subject Refusal
4. Clinical/Site Error
5. Laboratory Error
6. Investigator/Staff decision
7. Other

Subsets of the protocol deviations can be identified as major and minor protocol deviation as described below:

Major Protocol Deviation: A protocol deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

Minor Protocol Deviation: A protocol deviation that will not significantly affect the completeness, accuracy, and/or reliability of the study data and that will not significantly affect a subject's rights, safety, or well-being.

Upon soft lock of database, all documented protocol deviations in the study will be reviewed to identify all major and minor protocol deviations by a data review team including representatives from DPC clinical operations, medical, data management, and statistics, and sent to the sponsor for approval. Final decisions will be documented in the eTMF and incorporated into the CDISC datasets (SDTM DV and ADaM ADDV).

All protocol deviations will be listed. A separate listing will include only the major protocol deviations.

The following protocol deviation summaries will be tabulated by cohort (Cohort 1 wAIHA / Cohort 2 CAD) for Part A + B and Part B. The study part will be determined by the protocol deviation start date, i.e. protocol deviations that began at any point during Part A or Part B will be

summarized in Part A + B and protocol deviations that began on or after the date of first 1080 mg APL-2 dose (Part B Study Day 1) will be summarized in Part B.

- ***Part A + B:***
  - The number of deviations and number/proportion of subjects with protocol deviations during Part A + B and with major protocol deviations during Part A + B.
  - The number of deviations and number/proportion of subjects with each protocol deviation category during Part A + B.
- ***Part B:***
  - The number of deviations and number/proportion of subjects with protocol deviations during Part B and with major protocol deviations during Part B.
  - The number of deviations and number/proportion of subjects with each protocol deviation category during Part B.

5.1.3 Demographics and Baseline Characteristics

The following demographics will be tabulated by cohort (Cohort 1 wAIHA / Cohort 2 CAD) using summary statistics for continuous parameters and frequency/percent for categorical parameters at Part A Core Study Phase Baseline for Safety/PP Analysis Set:

- Age
- Sex
- Race
- Ethnicity
- Baseline Height
- Baseline Weight
- Baseline BMI

The following baseline characteristics will be tabulated using summary statistics for continuous parameters and frequency/percent for categorical parameters as well:

- Time since diagnosis of wAIHA or CAD
- CH50
- AH50
- Complement C3
- C3d Type I, Type II, Type III
- Reticulocytes
- Haptoglobin
- Hemoglobin
- Anaemia categories (Mild: Hemoglobin ≥ 10 / Moderate: 5 ≤ Hemoglobin < 10 / Severe: Hemoglobin < 8)
- Plasma Hemoglobin
- Direct Antiglobulin Test (Negative / Positive)
- Baseline Cold Agglutinins (< 1:32 / 1:128 / 1:256 / 1:512 / > 1:512)
- Anti-C3 Coombs (Negative / WKPOS / 1+POS / 2+POS / 3+POS / 4+POS)
- Number of Transfusions Per Month in 12 Months Prior to First Dose (derived as the number of Packed Red Blood Cell transfusions in the 365 days prior to first APL-2 dose*365/28)

5.1.4 Medical and Surgical History

Medical and Surgical history was collected at Screening. All medical/surgical history data and ongoing medical history will be listed and summarized at Part A + B Baseline for the Safety and PP Analysis Sets by the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 System Organ Class (SOC) and Preferred Term (PT) and by cohort (wAIHA / CAD).

5.1.5 Prior and Concomitant Medications

5.1.5.1 *Prior and Concomitant Derivations*

Prior and concomitant medications will be coded to the therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug Dictionary (WHODrug) classifications version March 2021.

Prior medications will include any medications reported with a start date prior to the subject taking their first study dose of Part A Core Study and will be summarized by WHODrug Anatomical Therapeutic Chemical (ATC) Class 3 Term and WHODrug Preferred Name.

Concomitant medications (CM) will include any medications being taken after the subject starts their study medication and will also be summarized by WHODrug ATC Class 3 Term and WHODrug Preferred Name. Hence, medications ongoing at the start of dosing will be counted in both the prior and concomitant medication summaries. Further categorization for concomitant medications will be included in the analysis:

- ***Part A + B CM***: Any medication taken during Part A or Part B of the study. This can include prior medications that were continued into Part A and Part B of the study
- ***Part B CM***: Any medication taken during Part B of the study. This can include prior medications that were taken continuously into Part B of the study. Concomitant medications taken in Part A but ended prior to Part B will not be considered as concomitant medications during Part B.

For the purposes of determining prior/concomitant medications and study part, if a partial date is recorded, the following convention will be used to assign the medication dates:

- 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.

5.1.5.2 *Medication Listings*

All prior medications and concomitant medications, interventions and procedures will be presented in listings for all subjects in Safety Set.

The categorization of concomitant medications (CM Part A + B / CM Part B) will be included in the listings.

5.1.5.3 *Medication Summary Tables*

The following summaries will be tabulated:

- Prior Medications, subjects who had medications prior to entering Part A Core Study Phase in the Safety Set:
    - Frequency of subjects taking prior medications by WHODrug ATC Class 3 and Preferred Name, and by cohort
- Concomitant Medications:
    - ***Part A + B:***
        - For concomitant medications taken during Part A or Part B: Frequency of subjects by concomitant medication WHODrug ATC Class 3, Preferred Name, and by cohort
    - ***Part B:***
        - Frequency of subjects by concomitant medication WHODrug ATC Class 3, Preferred Name, and by cohort

5.1.6 Exposure

All study drug exposure data will be listed based on the Study Drug Administration eCRF.

5.1.6.1 *Compliance Derivations*

The compliance for Part A + B must incorporate the different dosing regimens of the daily APL-2 dosing regimen (Part A) and the twice/three times weekly APL-2 dosing regimen (Part B).

Part A Compliance

For Part A, compliance will be calculated as:

$$Part\ A\ Compliance = \frac{number\ of\ complete\ study\ doses\ administered\ during\ Part\ A}{total\ expected\ study\ doses\ during\ Part\ A} x\ 100$$

Unless otherwise noted, during the Part A Core Study Phase, the number of expected doses is the number of days during Part A for subjects that did not roll over into Part B. For subjects that rolled over into Part B, the expected number of doses is the number of days during Part A – 1 to account for the skipped dose prior to the dose transition

Part B Compliance

For the Part B, compliance will be calculated as:

$$Part\ B\ Compliance = \frac{number\ of\ complete\ study\ doses\ administered\ during\ Part\ B\ prior\ to\ study\ discontinuation/completion}{total\ number\ of\ expected\ study\ doses\ during\ Part\ B} x\ 100$$

That is, when subjects receive twice weekly dosage, percentage compliance will be calculated as:

$$Part\ B\ Compliance = \frac{actual\ number\ of\ complete\ study\ doses\ administered}{(\text{last dose date} - \text{first dose date} + 3.5)/7)\ \text{x}\ 2} x\ 100$$

When subjects receive every 3 days dosage, percentage compliance will be calculated as:

$$Part\ B\ Compliance = \frac{actual\ number\ of\ complete\ study\ doses\ administered}{\frac{\text{last dose date} - \text{first dose date}}{3} + 1} x\ 100$$

Part A + B Compliance

Using the above, the compliance during Part A + B period will be calculated as:

$$Part\ A\ +\ B\ Compliance = \frac{number\ of\ complete\ study\ doses\ administered\ during\ Part\ A + number\ of\ complete\ study\ doses\ administered\ during\ Part\ B}{total\ number\ of\ expected\ study\ dosesduring\ Part\ A + total\ number\ of\ expected\ study\ doses\ druing\ Part\ B} x\ 100$$

5.1.6.2 ***Exposure and Compliance Listings***

All APL-2 Study Drug administration and Drug accountability will be listed. Compliance during Part A + B and Part B will be listed by subject.

5.1.6.3 ***Exposure and Compliance Summary Tables***

The following exposure and compliance parameters will be summarized by Part A + B and Part B and cohort (Cohort 1 wAIHA / Cohort 2 CAD):

- Total dose administered summary statistics
- Duration (total dosing period in days) summary statistics
- Compliance summary statistics
- Compliance frequency categories (Compliance < 80% / 80% ≤ Compliance < 90% / 90% ≤ Compliance < 100% / 100% ≤ Compliance < 120%

5.2 Safety Analysis

The primary objective of the study is to assess the safety and tolerability of APL-2. The safety analyses will be performed on Safety Set per the specifications outlined in the subsections below.

5.2.1 Adverse Events

5.2.1.1 *Treatment-Emergent Adverse Events (TEAE)*

TEAEs are defined as those AEs that occur after Dosing on Day 1, or worsen in severity, and up to 8 weeks (56 days) after the last dose of APL-2.

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 56 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.

5.2.1.2 *Treatment-Emergent Adverse Event Study Part*

TEAE will be summarized by study part in Safety Set using the following definitions:

- ***Part A + B***: will include all TEAE from a start date on or after the first dose of APL-2 in Part A up to 8 weeks (56 days) after the last

dose of APL-2 in Part B.

- ***Part B***: will include all TEAE during Part B which is any AE with a start date on or after the date of first 1080 mg APL-2 dose up to the end of 8 weeks (56 days) after the last dose of APL-2 in Part B.

5.2.1.3 *Adverse Events of Special Interest and Special Search Categories*

Version 23.0 of MedDRA will be used to classify all AEs. Per Protocol Version 1 Amendment 4, Protocol Adverse Events of Special Interest (AESI) include the following categories and Standardized MedDRA Queries (SMQ):

- Local or systemic infection of any origin (AE SOC = "Infections and Infestations")
- Clinically significant decrease in kidney function, defined as AE SOC = "Renal and Urinary Disorders" or AE SOC = "Investigations" with AE PT = "Blood Creatinine Increased Creatinine"
- Injection site reactions (as collected in eCRF)
- Thrombotic events (Thrombophlebitis SMQ = 20000081 or AEHLGTCD = 10014523, Embolic and Thrombotic Events SMQ = 20000115)

Additionally, the following TEAE Special Search Categories will include the following:

- Haemolytic Disorders (SMQ = 20000019)
- Hypersensitivity (SMQ = 20000214)
- Sepsis (SMQ =20000234)
- Infections (any AE under AESOC = "Infections and Infestations")
- Thrombosis (Thrombophlebitis SMQ = 20000081 or AEHLGTCD = 10014523, Embolic and Thrombotic Events SMQ = 20000115)

AESIs will be determined by a review of all AEs by the clinical and data management study staff. This review will allow for the inclusion of AEs of special interest arising during the study that are not on the above list, based on a clinical decision. It is expected that documentation of the AEs of special interest will be maintained outside the Medrio database system by the biostatistics and data management staff (with review by medical) and used by the programmer for analysis of the AEs of special interest.

5.2.1.4 *Time to Onset and Exposure Adjusted Incidence*

For summary tables that summarize time-at-risk exposure adjusted incidence, the following definitions will be used.

Part A + B:

Part A + B Exposure-adjusted incidence (EAI) of an AE event is defined as the number of events divided by the total duration of exposure of the subjects at risk during the entire Part A + B treatment, which is computed as following:

$$\textit{Part A + B Exposure Adjusted incidence rate (e)} = n*100/EY_{A+B}$$

where:

- *n* is the number of subjects *with an event*
- *Exposure year* (EY_{A+B}) *= (sum of time to onset of the event)/365.25*
- *Time to onset of the event = date of onset of event – date of the first APL-2 dose +1*

For subjects without the event, time to onset is censored as follows:

Time to onset of the event = last dose date + 56 days – first APL-2 dose date +1

For subjects who experienced the same event on multiple occasions:

Time to onset of the event = date of onset at the first occasion – first APL-2 dose date +1

Part B:

Part B EAI will be determined for Part B TEAE (i.e. AE with a start date on or after the date of first 1080 mg APL-2 dose). It is defined as the number of events divided by the total duration of exposure of the subjects at risk during Part B treatment, which is computed as following:

*Part B Exposure Adjusted incidence rate (e) = n*100/EY_B*

where:

- *n* is the number of subjects with an event
- *Exposure year (EY_B) = (sum of time to onset of the event)/365.25*
- *Time to onset of the event = date of onset of event – date of the first 1080 APL-2 dose +1*

For subjects without the event, time to onset is censored as follows:

Time to onset of the event = last dose date + 56 days – first 1080 mg APL-2 dose date +1

For subjects who experienced the same event on multiple occasions:

Time to onset of the event = date of onset at the first occasion – first 1080 mg APL-2 dose date +1

5.2.1.5 ***Adverse Event Listings***

An AE data listing of all AEs collected on study, including verbatim term, preferred term, treatment, severity, and relationship to treatment will be provided. Serious Adverse Events (SAEs), adverse events of special interest, and details of subjects withdrawing due to adverse events will also be listed. A Study Day in Part A + B relative to Part A Baseline, a

Study Day in Part B relative to Part B Baseline, and the duration of AEs will be included in listings.

5.2.1.6 ***Adverse Event Summary Tables***

Adverse Event tables will include summaries for TEAE in Part A + B and for TEAE in Part B.

Overall Summary Table

An overall AE summary will present the number of events and the frequency of subjects by cohort and by study part (Cohort 1 wAIHA Part A + B / Cohort 1 wAIHA Part B / Cohort 2 CAD Part A + B / Cohort 2 CAD Part B) with the following categories:

- any TEAE
- any TEAE considered as least possibly related to study drug (evaluated by the investigator as Possibly Related, Probably Related, Definitely Related, or Unknown)
- any serious TEAE
- Maximum severity TEAE of mild, moderate, severe, life threatening, and death, i.e. a subject with TEAEs at different intensities will be summarized at the most severe intensity
- any TEAE of special interest
- any TEAE leading to study drug discontinuation
- any TEAE leading to death

The total number of unique terms within subjects will also be presented in each of the categories above, counting each TEAE PT only once within each subject. Additionally, the total number of unique terms within cohorts will be presented in each of the categories above, counting each TEAE PT only once within each cohort.

Summary Tables by SOC and PT

The following tables will be presented with the number of events and the number/percent of subjects by cohort and by study part (Cohort 1

wAIHA Part B / Cohort 1 wAIHA Part A+ B / Cohort 2 CAD Part B / Cohort 2 CAD Part A + B).

- Non-ISR TEAEs by SOC and preferred term, including exposure-adjusted incidence
- TEAEs regarded as at least possibly related to study drug by SOC and preferred term, including exposure-adjusted incidence
- Injection Site Reaction TEAEs by SOC and preferred term, including exposure-adjusted incidence
- Serious AEs by SOC and preferred term, including exposure-adjusted incidence

The summaries above will be ordered by alphabetical SOC and descending order of total event count of the term in Part A + B for the PT within each SOC.

Summary Tables by SOC, PT, and Maximum Severity

The following will also be tabulated with the number/percent of subjects by cohort and study part (wAIHA Part B / wAIHA Part A + B / CAD Part B / CAD Part A + B):

- TEAEs by SOC, preferred term, and maximum severity
- Serious TEAE by SOC, preferred term, and maximum severity
- TE Protocol AESIs by SOC, preferred term, and maximum severity
- Related TE Protocol AESIs (regarded as at least possibly related to study drug) by SOC, preferred term, and maximum severity
- TEAE of Special Search Categories by SOC, preferred term, and maximum severity
- Related TEAE of Special Search Categories (regarded as at least possibly related to study drug) by SOC, preferred term, and maximum severity

The summaries above will be ordered alphabetical SOC and alphabetical PT within each SOC.

5.2.2 Clinical Laboratory Tests

5.2.2.1 *Clinical Laboratory Normalization*

Some laboratory parameters will be collected by central and local laboratories. In the cases where a visit's sample is collected on both central and local labs, the central lab result will be presented in the TLF. In the cases where only local labs are available, the local lab data will be normalized using the method developed by Stein (Stein, 1992, 2001).

The procedure for the normalization of local lab results will be followed for all local lab values with different normal ranges than the central lab:

1. Convert all parameters' units from different local lab units to SI units.

2. Impute the local normal ranges as shown below.

3. Assume there is one central Lab (LabConnect) and all NRLO(CL) and NRHI(CL) are sourced from Appendix IV of LabConnect's Central Scope of Work 1.0 11 July 2017 and gender/age specific normal ranges are used when applicable.

   i. If the NRLO is missing and NRHI is not missing, then do the following:

   *NRLO=NRHI * NRLO(CL) / NRHI(CL)*

   ii. If the NRHI is missing and NRLO is not missing, then do the following:

   *NRHI=NRLO * NRHI(CL) / NRLO(CL)*

   iii. If both NRLO and NRHI are missing prior to the imputations above, do the following:

   NRLO=min (all NRLO including CL)

   and

   NRHI=max (all NRHI including CL),

using sex- or age-specific normal ranges when applicable

4. The following formula will be used to convert local lab value at observation level to central lab value:

$$Central\ value\ = NRLO(CL) + \frac{local\ value - NRLO}{NRHI - NRLO} \times (NRHI(CL) - NRLO(CL))$$

where:

- *NRLO*: Low normal range for local lab
- *NRHI*: High normal range for local lab
- *NRLO(CL):* Low normal range for central lab
- *NRHI(CL):* High normal range for central lab

5. Check for negative Lab values after the normalization. If so, do the following:
   a. Set negative value to Zero, or
   b. Use Upper Scale Formula: *Central Value = Local value * NRHI (CL)/ NRHI*, or
   c. Use Lower Scale Formula: *Central Value = Local value * NRLO (CL)/ NRLO*

   (Use a, or b or c as appropriate).

6. Perform the analyses (e.g., CFB) as usual.

5.2.2.2 Potentially Clinically Significant

Clinical laboratory test values are potentially clinically significant (PCS) if they meet either the low or high PCS criteria listed in Table 3 below.

Table 3: Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	Criteria
Hematology	
WBC (total) (x10^9/L)	<3.0 > 16
Lymphocyte (x10^9/L)	< 0.5 < 0.8 > 12
Neutrophils (x10^9/L)	< 1.0 < 1.5 > 12
RBC (x10^12/L)	< 3.3 > 6.8
Hemoglobin (g/dL)	< 10
Platelet count (x10^9/L)	< 100 > 600
Serum Chemistry	
ALT	> 1.5xULN > 3.0xULN
AST	> 1.5xULN > 3.0xULN
Total Serum Bilirubin	> 1.5xULN
GGT	> 1xULN
ALT or AST > 3xULN and concurrent elevated total bilirubin defined as	> 1.5xULN > 2.0xULN

For all other serum chemistry, coagulation, and urinalysis parameters, abnormal values per the central lab reference range (for central lab results) or normalized reference ranges (for normalized lab results) will be used as potentially clinically significant.

5.2.2.3 Clinical Laboratory Listings

Non-efficacy Chemistry, Non-efficacy Hematology, Coagulation, Urinalysis, non-PD Cytometry, and Miscellaneous (which includes the Anti-APL-2 AB

Assay) results will be listed for Safety Set. Additionally, separate PCS listings for subjects with at least one PCS result will be presented for each of the above laboratory categories.

Listings of all lab results with their corresponding changes from baseline (Change from Part A + B Baseline and Change from Part B Baseline for assessments after the first 1080 mg APL-2 dose) will be presented. Change from Part A + B Baseline will be considered as the pre-dose measure on Study Day 1, or the screening assessment if missing the Study Day 1 assessment. Part B Baseline will be considered as the last assessment before the first 1080mg APL-2 dose for each subject. Potentially Clinically Significant laboratory values will be identified in listings per Section 5.2.2.2, using high and low flags.

5.2.2.4 Clinical Laboratory Summary Tables

Non-efficacy Chemistry, Non-efficacy Hematology, Coagulation, Urinalysis, non-PD Cytometry, and Miscellaneous results will be summarized separately.

Descriptive Statistics:

Descriptive statistics will be presented by cohort (Cohort 1 wAIHA / Cohort 2 CAD) on Safety Set as follows:

- ***Part A + B***: Part A + B Baseline, all post-baseline scheduled visits through the end of study, and change from Part A + B Baseline.
- ***Part B***: Part B Baseline, all scheduled visits in Part B (i.e. on and after the first 1080 mg APL-2 dose), and change from Part B Baseline.

PCS Frequencies:

The frequency of PCS values at all scheduled visits on-study will be presented by cohort (Cohort 1 wAIHA / Cohort 2 CAD) on the safety set. At each visit, the number of subjects evaluable will be presented with the frequency and percent of subjects with low, normal, and high PCS results. The percentages will be calculated relative to the number of subjects with available baseline values and at least 1 post-baseline assessment. The numerator is the total

number of subjects by-visit with at least 1 post-baseline PCS value and denominator is the number of subjects with evaluable assessment in the cohort at the respective visit.

5.2.3 Vital Signs

5.2.3.1 *Potentially Clinically Significant*

Vital sign values are potentially clinically significant (PCS) if they meet either the low or high PCS criteria listed in Table 4 below.

Table 4: Criteria for Potentially Clinically Significant Vital Signs

Value	Parameter	Low	High
Observed	Systolic Blood Pressure (mmHg)	≤ 80	≥165
	Diastolic Blood Pressure (mmHg)	≤ 40	≥ 95
	Pulse (bpm)	≤ 40	≥120
	Temperature (ºC)		≥ 38

*mmHg=millimeters of mercury, bpm=beats per minute, °C=degrees Celsius

5.2.3.2 *Vital Signs Listings*

Listings of all vital sign results with their corresponding changes from baseline (Change from Part A + B Baseline and Change from Part B Baseline for assessments after the first 1080 mg APL-2 dose) will be presented. Change from Part A + B Baseline will be considered as the last pre-dose measure on Study Day 1, or the screening assessment if missing the Study Day 1 assessment. Part B Baseline will be considered as the last assessment before the first 1080mg APL-2 dose for each subject. Potentially Clinically Significant vital sign values will be identified in listings per Section 5.2.3.1 above, using high and low flags.

5.2.3.3 ***Vital Signs Summary Tables***

Descriptive Statistics:

Descriptive statistics will be presented by cohort (Cohort 1 wAIHA / Cohort 2 CAD) on Safety Set as follows:

- ***Part A + B***: Part A + B Baseline, all post-baseline scheduled visits through the end of study and change from Part A + B Baseline.
- ***Part B***: Part B Baseline, all scheduled visits in Part B (i.e. on and after the first 1080 mg APL-2 dose), and change from Part B Baseline.

PCS Frequencies:

The frequency of PCS values at all scheduled visits on-study will be presented by cohort (Cohort 1 wAIHA / Cohort 2 CAD) on the safety set. At each visit, the number of subjects evaluable will be presented with the frequency and percent of subjects with low, normal, and high PCS results. The percentages will be calculated relative to the number of subjects with available baseline values and at least 1 post-baseline assessment. The numerator is the total number of subjects by-visit with at least 1 post-baseline PCS value and denominator is the number of subjects with evaluable assessment in the cohort at the respective visit.

5.2.4 Electrocardiogram (ECG)

ECG data is not scheduled to be collected in Part B Long-term Extension Phase; therefore, ECG summaries will not be summarized. ECG data that was collected after visit 15 of Part A will be presented in listings.

5.2.5 Physical Examination

Physical examination data will be summarized in listing(s).

5.3 Exploratory Efficacy and Pharmacodynamic Analyses

While the primary objective of this study is safety, exploratory efficacy and pharmacodynamic analyses will be presented. All efficacy listings will include

all subjects in the Intent-to-Treat Set. All PD listings will include all subjects in the PD Set. All efficacy summaries will be evaluated on the Intent-to-Treat Set. All pharmacodynamic summaries will be evaluated on the PD Set.

5.3.1 Packed Red Blood Cell (PRBC) Transfusions

5.3.1.1 *Transfusions Per Month*

PRBC Transfusions per month will be derived for Part A + B Baseline, Part A + B, Part B Baseline, and Part B as follows:

- *Part A + B Baseline Transfusions Per Month =*

$$\frac{\#\ of\ transfusions\ in\ 365\ days\ prior\ to\ first\ APL{-}2\ dose * 28}{365}$$

- *Part A + B Transfusions Per Month =*

$$\frac{\#\ of\ transfusions\ during\ Part\ A\ and\ Part\ B * 28}{\#\ of\ days\ during\ Part\ A\ and\ Part\ B}$$

- *Part B Baseline Transfusions Per Month =*

$$\frac{\#\ of\ transfusions\ in\ 365\ days\ prior\ to\ first\ 1080\ mg\ APL{-}2\ dose * 28}{365}$$

- *Part B Transfusions Per Month =* $\frac{\#\ of\ transfusions\ during\ Part\ B * 28}{\#\ of\ days\ during\ Part\ B}$

5.3.1.2 *Units Per Month*

PRBC units per month will be derived for Part A + B Baseline, Part A + B, Part B Baseline, and Part B as follows:

- *Part A + B Baseline Units Per Month =*

$$\frac{\#\ of\ units\ in\ 365\ days\ prior\ to\ first\ APL{-}2\ dose * 28}{365}$$

- *Part A + B Units Per Month =*

$$\frac{\#\ of\ units\ during\ Part\ A\ and\ Part\ B * 28}{\#\ of\ days\ during\ Part\ A\ and\ Part\ B}$$

- *Part B Baseline Units Per Month =*

$$\frac{\#\ of\ units\ in\ 365\ days\ prior\ to\ first\ 1080\ mg\ APL{-}2\ dose * 28}{365}$$

- *Part B Units Per Month* $= \frac{\#\ of\ units\ during\ Part\ B * 28}{\#\ of\ days\ during\ Part\ B}$

5.3.1.3 ***Transfusions Listings***

The following listings will be prepared:

- Transfusion History, for all transfusions recorded in the 365 days prior to enrollment
- On-Study Transfusions, for all transfusions recorded on-study, where study part will be specified
- PRBC Transfusions and Units Per Month which will include:
  - ***Part A + B PRBC***:
    - Number of Days during Part A + B Baseline Period (365 days) and Number of Days during Part A and B
    - Part A + B Baseline Transfusions Per Month and Part A + B Transfusions Per Month
    - Part A + B Baseline Units Per Month and Part A + B Units Per Month
  - ***Part B PRBC***:
    - Number of Days during Part B Baseline Period (365 days) and Number of Days during Part B
    - Part B Baseline Transfusions Per Month and Part B Transfusions Per Month
    - Part B Baseline Units Per Month and Part B Units Per Month

5.3.1.4 ***Transfusions Summary Tables***

The following tabular summaries will be prepared:

- ***Part A + B PRBC***: Summary statistics will be prepared by Cohort (Cohort 1 wAIHA / Cohort 2 CAD) for the ITT Set and Per Protocol Set who have Part A + B Baseline or at least one post-Part A + B Baseline PRBC transfusion during Part A + B phase:
    - Part A + B Baseline Transfusions Per Month
    - Part A + B Transfusions Per Month
    - Part A + B Baseline Units Per Month
    - Part A + B Units Per Month
- ***Part B PRBC***: Summary statistics will be prepared by Cohort (Cohort 1 wAIHA / Cohort 2 CAD) for the ITT Set and Per Protocol Set who have Part B Baseline or at least one post-Part B Baseline PRBC transfusion during Part B Phase:
    - Part B Baseline Transfusions Per Month
    - Part B Transfusions Per Month
    - Part B Baseline Units Per Month
    - Part B Units Per Month

5.3.2 Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale

5.3.2.1 ***FACIT Fatigue Score***

The FACIT Fatigue Scale (Version 4) questionnaire is an exploratory efficacy endpoint. 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 Item Codes 5 and 7 of the FACIT Fatigue Scale Version 4) are reversed to ensure that the higher score corresponds to a higher quality of life.

Study Day 1 will be considered the Part A+ B Baseline for the FACIT assessment. If this is missing, change from Part A + B baseline will not be calculated. Part B Baseline will be considered as the last assessment before the first 1080mg APL-2 dose for each subject.

The FACIT and all related works are owned and copyrighted by, and the intellectual property of PPD, Ph.D. Permission for use of the FACIT-FATIGUE questionnaire is obtained by contacting PPD at information@facit.org.

5.3.2.2 ***FACIT Listings***

The following listings will be prepared:

- FACIT Fatigue Scale Questionnaire Responses
- FACIT Fatigue Score and Change from Baseline which will include:
  - ***Part A + B***:
    - FACIT Fatigue Score Results at all Part A + B visits with Change from Part A + B Baseline and Percent Change from Part A + B Baseline
  - ***Part B***:
    - FACIT Fatigue Score Results at all Part B visits with Change from Part B Baseline and Percent Change from Part B Baseline

5.3.2.3 ***FACIT Summary Tables***

The following tabular summaries will be prepared by Cohort (Cohort 1 wAIHA / Cohort 2 CAD) for ITT Set and Per Protocol Set for the following:

- ***Part A + B FACIT Fatigue Score***::
    - FACIT Fatigue Score results at all scheduled visits through Part A Visit 15 and from Part B Baseline through the end of study
    - Change from Part A + B Baseline FACIT Fatigue Score at all post-baseline visits through Part A Visit 15 and from Part B Baseline through end of study
    - Percent Change from Part A + B Baseline FACIT Fatigue Score at all post-baseline visits through Part A Visit 15 and from Part B Baseline through end of study
- ***Part B FACIT Fatigue Score***:
    - FACIT Fatigue Score results at Part B Baseline and all scheduled Part B visits
    - Change from Part B Baseline FACIT Fatigue Score ay all post-baseline visits
    - Percent Change from Part B Baseline FACIT Fatigue Score at all post-baseline visits

5.3.2.4 ***FACIT Summary Figures***

The following figures will be prepared:

- ***Part A + B FACIT Fatigue Score***: Mean score ± SE will be presented by Cohort (Cohort 1 wAIHA / Cohort 2 CAD) for the ITT Set and Per Protocol Set for the following:
    - FACIT Fatigue Score results at all scheduled visits through Part A Visit 15 and from Part B Baseline through end of study

- Change from Part A + B Baseline FACIT Fatigue Score at all post-baseline visits through Part A Visit 15 and from Part B Baseline through end of study

- ***Part B FACIT Fatigue Score***:
  - Change from Part B Baseline FACIT Fatigue Score from Part B Baseline through end of study

5.3.3 Linear Analog Self-Assessment (LASA)

5.3.3.1 *LASA Overall Quality of Life and Subscales*

The LASA, which consists of five single statements asking respondents to rate, on zero to ten scales, their perceived level of functioning (see Protocol Section 17.2).

Specific domains include physical well-being (i.e., fatigue, activity level), emotional well-being (i.e., depression, anxiety, stress), spiritual well-being (i.e., sense of meaning), and intellectual well-being (i.e., ability to think clearly, concentrate). An item for overall quality of life (QoL) is also included. The Likert scales run from 0 (as bad as it can be) to 10 (as good as it can be), where higher ratings suggest higher QoL.

Study Day 1 will be considered the Part A+ B Baseline for the LASA assessment. If this is missing, change from Part A + B baseline will not be calculated. Part B Baseline will be considered as the last assessment before the first 1080mg APL-2 dose for each subject.

5.3.3.2 *LASA Listings*

The following listings will be prepared:

- LASA Domain Responses (Physical Well Being, Emotional Well Being, Spiritual Well Being, Intellectual Well Being, and Overall Quality of Life) and Change from Baseline which will include:

- ***Part A + B***:
  - LASA Domain Results at all Part A + B visits with Change from Part A + B Baseline and Percent Change from Part A + B Baseline
- ***Part B***:
  - LASA Domain Results at all Part B visits with Change from Part B Baseline and Percent Change from Part B Baseline

5.3.3.3 ***LASA Domain Summary Tables***

The following tabular summaries will be presented for each of the LASA Domains (Overall Quality of Life, Physical Well Bring, Emotional Well Being, Spiritual Well Being, and Intellectual Well Being) by Cohort (Cohort 1 wAIHA / Cohort 2 CAD) for the ITT Set and Per Protocol Set for the following:

- ***Part A + B LASA Domain Scores***:
  - LASA Domain Score results at all scheduled visits through Part A Visit 15 and from Part B Baseline through end of study
  - Change from Part A + B Baseline LASA Domain Score at all post-baseline visits through Part A Visit 15 and from Part B Baseline through end of study
  - Percent Change from Part A + B Baseline LASA Domain Score at all post-baseline visits through Part A Visit 15 and from Part B Baseline through end of study
- ***Part B LASA Domain Scores***:
  - LASA Domain Score results at Part B Baseline and all scheduled Part B visits

- Change from Part B Baseline LASA Domain Score at all post-baseline visits
- Percent Change from Part B Baseline LASA Domain Score at all post-baseline visits

5.3.3.4 ***LASA Domain Summary Figures***

The Mean score ± SE figures will be presented for each of the LASA Domains (Overall Quality of Life, Physical Well Bring, Emotional Well Being, Spiritual Well Being, and Intellectual Well Being) by Cohort (Cohort 1 wAIHA / Cohort 2 CAD) for the ITT Set and Per Protocol Set for the following:

- ***Part A + B LASA Domain Scores***:
  - LASA Domain Score results at all scheduled visits through Part A Visit 15 and from Part B Baseline through end of study
  - Change from Part A + B Baseline LASA Domain Score at all post-baseline visits through Part A Visit 15 and from Part B Baseline through end of study
- ***Part B LASA Domain Scores***:
  - Change from Part B Baseline LASA Domain Score from Part B Baseline through end of study

5.3.4 Efficacy Laboratory Parameters

5.3.4.1 ***Parameters and Normalization***

Efficacy laboratory parameters include the following:

1. Lactate Dehydrogenase
2. Reticulocytes
3. Hemoglobin
4. Haptoglobin
5. Indirect Bilirubin

Study Day 1 will be considered the Part A+ B Baseline for the efficacy lab assessments. If this is missing, the screening assessment, if available, will be used as Part A + B Baseline. Part B Baseline will be considered as the last assessment before the first 1080 mg APL-2 dose for each subject.

Some laboratory parameters will be collected by central and local laboratories. In the cases where a visit's sample is collected on both central and local labs, the central lab result will be presented in the TLF. In the cases where only local labs are available, the local lab data will be normalized using the procedure outlined in Section 5.2.2.1.

5.3.4.2 ***Efficacy Laboratory Listings***

The following listings will be prepared:

- Efficacy Laboratory Results and Change From Baseline will be presented in separate listings which will include:
  - ***Part A + B***:
    - Lab Results at all Part A + B visits with Change from Part A + B Baseline and Percent Change from Part A + B Baseline
  - ***Part B***:
    - Lab Results at all Part B visits with Change from Part B Baseline and Percent Change from Part B Baseline

5.3.4.3 ***Efficacy Laboratory Summary Tables***

The following tabular summaries will be presented for each efficacy laboratory parameter by Cohort (Cohort 1 wAIHA / Cohort 2 CAD) for the ITT Set and Per Protocol Set for the following:

- ***Part A + B Lab Results***:
    - Lab results at all scheduled visits through Part A Visit 15 and from Part B Baseline through end of study
    - Change from Part A + B Baseline lab result at all post-baseline visits through Part A Visit 15 and from Part B Baseline through end of study
    - Percent Change from Part A + B Baseline lab result at all post-baseline visits through Part A Visit 15 and from Part B Baseline through end of study
- ***Part B Lab Results***:
    - Lab results at Part B Baseline and all scheduled Part B visits
    - Change from Part B Baseline lab result at all post-baseline visits
    - Percent Change from Part B Baseline lab result at all post-baseline visits

5.3.4.4 ***Efficacy Laboratory Summary Figures***

The Mean result ± SE will be presented by cohort (Cohort 1 wAIHA / Cohort 2 CAD) for each of the laboratory parameters for the ITT Set and Per Protocol Set as the following:

- ***Part A + B Lab Results***:
    - Lab results at all scheduled visits through Part A Visit 15 and from Part B Baseline through end of study
    - Change from Part A + B Baseline lab result at all post-baseline visits through Part A Visit 15 and from Part B Baseline through end of study

- ***Part B Lab Results***:
    - Change from Part B Baseline lab results at all post-baseline visits

5.3.5 Pharmacodynamics

5.3.5.1 ***Parameters***

PD parameters include the following:

1. Complement CH50
2. Complement AH50
3. Complement C3

Additional PD parameters also include the following:

- C3 deposition on RBCs
    - Percent Type I
    - Percent Type II
    - Percent Type III
    - Percent Type I+II
    - Percent C3d on RBC

where:

$$\%C3d\ on\ (Type\ I + II\ RBCs) = \frac{\begin{pmatrix} Events\ (C3d\ (CD59\ HighType1\ norm\ RBC)\ + \\ Events\ (C3d(CD59\ dim\ Type\ II\ RBC) \end{pmatrix}}{\begin{pmatrix} Events\ CD59\ high\ Type\ 1\ norm\ (RBC) + \\ Events\ CD59\ dim\ Type\ II\ (RBC) \end{pmatrix}}\ x\ 100$$

and where:

$$\%\ C3d\ on\ RBC\ = \frac{C3d + Gly\ RBC\ Events}{Gly + RBC\ Events}\ x\ 100$$

Study Day 1 will be considered the Part A+ B Baseline for the PD assessments. If this is missing, the screening assessment, if available, will be used as Part A + B Baseline. Part B Baseline will be considered as the last assessment before the first 1080mg APL-2 dose for each subject.

5.3.5.2 ***PD Listings***

The following listings will be prepared for the PD Set:

- PD Results and Change from Baseline will be presented in separate listings which will include:
    - ***Part A + B***:
        - PD Results at all Part A + B visits with Change from Part A + B Baseline and Percent Change from Part A + B Baseline
    - ***Part B***:
        - PD Results at all Part B visits with Change from Part B Baseline and Percent Change from Part B Baseline

5.3.5.3 ***PD Summary Tables***

- The following summary statistics will be presented for each of the PD parameters by Cohort (Cohort 1 wAIHA / Cohort 2 CAD) for the PD Set and Per Protocol Set for the following:
- ***Part A + B PD Results***:
    - Lab results at all scheduled visits through Part A Visit 15 and from Part B Baseline through end of study
    - Change from Part A + B Baseline lab result at all post-baseline visits through Part A Visit 15 and from Part B Baseline through end of study
    - Percent Change from Part A + B Baseline lab result at all post-baseline visits through Part A Visit 15 and from Part B Baseline through end of study
- ***Part B PD Results***:
    - Lab results at Part B Baseline and all scheduled Part B visits

- Change from Part B Baseline lab result at all post-baseline visits
- Percent Change from Part B Baseline lab result at all post-baseline visits

5.3.5.4 ***PD Summary Figures***

The following figures mean result ± SE will be presented by cohort (Cohort 1 wAIHA / Cohort 2 CAD) for each of the PD parameters (CH50, AH50, Complement C3, C3d Type I, C3d Type II, C3d Type I+II, and C3d on RBC) for the PD Set and Per Protocol Set:

- ***Part A + B PD Results***:
  - Lab results at all scheduled visits through Part A Visit 15 and from Part B Baseline through end of study
  - Change from Part A + B Baseline lab result at all post-baseline visits through Part A Visit 15 and from Part B Baseline through end of study
- ***Part B PD Results***:
  - Change from Part B Baseline lab results at all post-baseline visits

5.3.6 Anti-drug antibody Assay

This data will be presented in listings.

5.4 Pharmacokinetic Analysis

All summaries and analyses of the pharmacokinetic data will be based on the Pharmacokinetic Set.

5.4.1 Pharmacokinetic Concentration Summaries

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. For the computation of descriptive statistics, BLQ will be taken as zero, except for the calculation of the geometric mean where the LLOQ will be used.

A listing of all APL-2 concentrations will be presented by dose. The actual study time will be listed, along with the deviation and percent deviation from nominal time.

For Part A, APL-2 concentrations will be summarized by planned study visit windows using descriptive statistics by randomized dose group, actual dose at the time of the visit. That is, at each visit, the descriptive statistics will be presented for:

- All randomized 270mg dose group, regardless of current dose
- All randomized 360mg dose group, regardless of current dose
- Subjects randomized to 270mg and on 270mg dose at time of visit
- Subjects randomized to 360mg and on 360mg dose at time of visit

For Part B, APL-2 concentrations will be summarized by planned study visit windows using descriptive statistics by cohort. The number of subjects with a value > BLQ will also be tabulated.

If a subject discontinues APL-2 dosing, then concentrations from samples collected more than 1 day after the last dose will be excluded from calculations.

For Part A, Linear and log-linear (± SE) concentration profile plots against time will be produced for each dose group.

For Part B, Linear and log-linear (± SE) concentration profile plots against time will be produced for each cohort.

For all time on-study, individual plots will be presented for PK concentration by study day. The individual plots will include an overlay of APL-2 dosing, also aligned by study day.

5.4.2 Pharmacokinetic Parameters

For both Part A and Part B, the following PK parameter for APL-2 will be derived using actual sample times:

$C_{trough,max}$ Maximal observed serum concentration. As later PK samples are collected pre-dose this is termed maximal trough concentration.

$C_{trough,max}$ will be calculated for both 270 mg and 360 mg where subjects receive both doses during Part A, and for Part B

The derived PK parameter will be listed by cohort and dose (for $C_{trough,max}$). The PK parameter will also be summarized using descriptive statistics. Geometric mean and CV will be included in the descriptive statistics.

6. TESTING/QUALITY CONTROL PLAN AND SOFTWARE/SYSTEM

All statistical programs, excluding PK analysis programs, will be written in SAS® version 9.4. Statistical programs will be tested and reviewed for Quality Control (QC) by a second programmer/biostatistician not involved in the programming as per DPC's standard operating procedure (SOP). In addition, DPC's SOP will be followed to ensure that the information is complete, consistent, and accurately reflects the data stored in the database. Further all TLFs will undergo a QC process by an independent biostatistician/programmer to ensure that the information is complete, consistent, and accurately reflects the data.

6.1 Programming Specifications for TLFs

Appendix 8.1 provides a list of all the TLFs that are planned to be produced.

6.2 Formatting Conventions

The following formatting conventions will be used to output TLFs:

- TLFs are outputted by SAS Output Delivery System (ODS) into Rich Text Files (RTF) format.
- Tables and Listings will include borders around all headings and data cells.
- Output will be in landscape orientation with margins of 0.75 inches on bottom, left, and top, and 3/8 inch for right.
- The default font to be in tables/listings/figures will be Courier New.
- Preferred and minimum font size:

Portion of Output	Preferred	Minimum
Page Header	9 pt	8 pt
Title	9 pt	8 pt
Column header	9 pt	8 pt
Cells	9 pt	8 pt
Footnote	9 pt	8 pt
Page Footer	9 pt	8 pt

- Data will be centered within columns when the maximum length of the data being displayed is less than or equal to the maximum width of the

column heading. When the maximum length of the data being displayed exceeds the maximum width of the column heading, the data will be left-justified.

- Column headings should be in initial capital characters. For numeric variables, include "unit" in the column heading when appropriate.
- In figures, axes will be labeled appropriately.

6.3 Standard Text Conventions

6.3.1 Header

All output (table, listing, or figure) will have the following header, as applicable:

```
Apellis Pharmaceuticals, Inc.
Protocol: APL2-CP-AIHA-208                                    Page xx of XX
Part B Long-Term Extension Study Report
```

All output will have the date and time (date and time output was generated) and internal page number in the header. Tables/Listings/Figures should be internally paginated (i.e., page numbers should appear sequentially within each output).

6.3.2 Title

At least three (3) lines, in general, will be reserved for the entire title.

- The first line is for the table/listing/figure number;
- The second line is for the actual title; and
- The third line is reserved for the analysis set descriptor.

All titles will be centered, as shown in the following example:

```
Table 14.3.1.1
Topline Summary of Adverse Events
Safety Set
```

6.3.3 Footnotes

Unless otherwise specified, footnotes will appear on all pages within the tables and listings as follows:

- Footnotes will be in the format of "NOTE: then the footnotes", as shown in the following example:

- `NOTE: SD = Standard Deviation.`

- Each line of a complete footnote should end with a period.
- When an abbreviation (e.g. AE, SAE, etc.) appears first time in the whole set of TLFs for a study, a footnote should be provided at least once; and it is up to the study statistician, to decide whether there is a need to repeat the same footnote for the rest of TLFs.
- A footnote serves as a brief explanation/clarification /definition /concept of a flag symbol or a character, an abbreviation, a terminology, etc., that appears in or relates directly to the displayed content of a table/listing/figure.
- All footnotes will be at the lowest line of the page immediately above the footer. The footer will be directly on the line below the last footnote.
- For Tables, first footnote will provide source listings and/or analysis datasets names for cross-referencing.

6.3.4 Footer

The following footer should appear at the very bottom of each page of a table, a listing, or a figure generated in SAS in the lower left corner:

```
Program Name: PGNAME.sas; Creation Date and Time: DDMMMYYYY HH:MM
Data Lock DDMMMYYYY HH:MM - ADaM Generated DDMMMYYYY Proprietary and Confidential
```

where PGNAME = SAS program name.

6.4 Statistical Conventions

6.4.1 Statistics Reported

- Unless otherwise specified, the mean and SD will be displayed to one more decimal place than the original value, while minimum and maximum will be reported in the format of the original data, e.g.:

  Original: xx

  Mean and SD: xx.x

  Minimum and maximum: xx
- Use of N versus n:

  N = total number of subjects or subjects in the analysis set.

  n = total number of subjects or subjects in the specific category.
- Descriptive statistics in this template include: N, Mean, Median, SD, Minimum, and Maximum.
- Unless specified in the actual TLF shells for a study, all percentages will be rounded to 1 decimal place in all tables/listings/figures. Rounding will take place after all calculations have been performed.

6.4.2 Tables Summarizing Categorical Data

The following specifications apply to tables that summarize categorical data:

- If the categories of a parameter are ordered, then all categories between the maximum possible category and the minimum category will be included, even if n=0 for a given category between the minimum and maximum level for that parameter.
- If the categories are not ordered, then only those categories for which there is at least one subject represented will be included.
- A missing category will be added to any parameter for which information is not available for any subjects.
- If there were no subjects who met the condition, then a message will appear indicating that no subjects met the condition for inclusion in that table.

6.4.3 Subject Data Listings

In general, individual subject data listings will include the data of all non-screen failure subjects. However, if a subject data listing includes only subjects who met a certain condition, and there were no subjects who met that condition, then a "message" will appear indicating that no subjects met the condition for inclusion in that listing. Data listings will provide the derived study day of an assessment or event, where appropriate.

7. REFERENCES

ICH E3 (1995): Structure and Content of Clinical Study Reports. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

ICH E6 R2 (2016): Integrated Addendum to ICH E6(R1). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

ICH E9 (1998): Statistical Principles for Clinical Trials. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

MedDRA Version 23.0 (March 2020). International Federation of Pharmaceutical Manufacturers and Associations (IFPMA).

Novel Insights into the treatment of complement-medicated hemolytic anemia. Berentsen S et al, (2019). Therapeutic Advances in Hematology. Vol 10: 1-20.

SAS® for Windows® Version 9.4. SAS Inc. Cary, North Carolina USA.

The WHO Drug Dictionary (WHO-DD) (March 1, 2021). World Health Organization (WHO) Uppsala Monitoring Center (UMC).