Statistical Analysis Plan

Study Title:	An Open Label, Single and Multiple Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of APL-2 as an Add-On to Standard of Care in Subjects with Paroxysmal Nocturnal Hemoglobinuria (PNH)
Protocol Number:	APL-CP0514 Version 4.0, Amendment 7 / 15 June 2017
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SIGNATORY PAGE

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REVISION HISTORY

Version No.	Version Date	Author	Description of Modifications
1.0	28 July 2015	PPD	Original Document
2.0	22 December 2016	PPD	Updates to account for changes introduced by Protocol 4.0 Amendment 3, Protocol 4.0 Amendment 4, and Protocol 4.0 Amendment 5
2.1	03 Feb 2017	PPD	Updates to account for changes introduced by Protocol Amendment 6; Additional FACIT and pharmacodynamic output added
3.0	07 Jun 2018	PPD	Updates to account for changes introduced by Protocol Amendment 7; added summary outputs of efficacy, PK, and PD for Cohort 4.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations and Acronyms	Description
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomic Therapeutic Chemical
AUC	Area Under the Curve
BLQ	Below Limit of Quantification
CS	Clinically Significant Abnormality
DMP	Data Management Plan
DPC	DP Clinical, Inc.
ECG	Electrocardiograms
eCRF	Electronic Case Report Form
FACIT	Functional Assessment of Chronic Illness Therapy
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ITT	Intent-To-Treat
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mmHg	Millimeter(s) of Mercury
msec	Millisecond(s)
NCS	Not Clinically Significant
ODS	Output Delivery System
OC	Oracle Clinical
QTcB	Heart Rate Corrected QT interval, Bazett's formula
QTcF	Heart Rate Corrected QT interval, Fridericia's formula
PD	Pharmacodynamics
PDF	Portable Document Format
PK	Pharmacokinetics
PI	Principal Investigator
PNH	Paroxysmal Nocturnal Hemoglobinuria

Abbreviations and Acronyms	Description
PRBC	Packed Red Blood Cells
PT	Preferred Term
QC	Quality Control
RBC	Red Blood Cell
RDC	Remote Data Capture
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedure
TLFs	Tables, Listings, and Figures
Th17	T-Helper 17 Cells
TEAE	Treatment Emergent Adverse Event
Treg	T-Regulatory Cells
ULN	Upper Limit of Normal
WHO	World Health Organization

1.0 Introduction

This Statistical Analysis Plan (SAP) provides 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 (TLFs) that will be produced and statistical methods that will be used are complete and accurate and will allow valid conclusions regarding the study objectives. In the development of this SAP, the following documents were used:

1. Protocol APL-CP0514 Version 4.0, Amendment 7, 15 June 2017
2. Protocol Administrative Clarification Memorandum, 12 July 2017
3. Electronic Case Report Form (eCRF), 23 December 2015
4. Electronic Case Report Form (eCRF), 27 September 2016
5. Electronic Case Report Form (eCRF), 10 August 2017

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

- ICH E3 (1996): Structure and Content of Clinical Study Reports
- ICH E6 (R2) (2016): Guideline for Good Clinical Practice
- ICH E9 (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 amendments to the SAP will be made prior to locking the database. Any additional analyses not described in the final analysis plan or deviations from the final analysis plan will be documented in the final clinical study report.

2.0 Study Overview

2.1 Study Objectives

The primary objectives of the study are to assess the safety, tolerability and pharmacokinetics (PK) of single and multiple subcutaneous (SC) doses of APL-2 in subjects with paroxysmal nocturnal hemoglobinuria (PNH) who are still anemic after treatment with eculizumab (Soliris®).

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

2.2 Study Design

This is a Phase 1, open-label, prospective, non-randomized, single and multiple ascending dose, first-in-human study in patients with PNH. The study is planned to enroll approximately 15 subjects across 4 cohorts. Cohorts 1-3 will comprise 2 subjects in each cohort. Cohort 4 will enroll sufficient subjects to ensure at least 6 subjects complete 28 days of dosing with APL-2. Subjects may participate in more than one cohort on the basis of medical benefit already experienced in the study.

Safety will be assessed throughout the study; serial blood samples and urine samples will be collected. Blood samples will also be collected for the PK assessment of APL-2 and for PD assessment. Cumulative data will be reviewed by a Safety Monitoring Committee (SMC) on a regular basis (Section 12). Interim PK analyses may be performed to reconsider the sampling time points as the study progresses and to guide the dose-escalation decision.

The screening period will be up to 30 days before the first dose. The planned length of participation (from Screening [Visit 1] to completion of the Exit visit) in the study for each subject is approximately 143 days for Cohorts 1 and 2 (30 day screen phase, 56 day treatment phase and 57 day follow-up), 115 days for Cohort 3 (30 day screen phase, 28 day treatment phase and 57 day follow-up) and 815 days for Cohort 4 (30 day screen phase, 729 day treatment phase and 56 day follow-up).

For Cohorts 1 and 2, subjects will receive a single SC dose of APL-2 on Study Day 1 (Visit 2). After a waiting period of at least 28 days, subjects may enter the multiple dose phase and receive SC APL-2 daily for 28 days at the corresponding multiple dose for their cohort. Dose escalation/new cohort initiation will only occur once all subjects in the preceding cohort have completed their 28-day waiting period.

Cohorts 3 and 4 will only undergo a multiple dose phase. Subjects will receive APL-2 for 28 days in Cohort 3. For Cohort 4, the treatment period will consist of four parts (Parts 1, 2A, 2B and 2C) - in Part 1, subjects will receive APL-2 for 28 days. On Day 29, subjects concluded to benefit from the treatment (as determined by the Investigator and Sponsor after reviewing the available data) will automatically enter into Part 2A and continue to receive daily doses of APL-2 until Day 84. If there is ongoing evidence of clinical benefit on Day 84 they may enter into Part 2B of the study, and continue receiving daily doses of APL-2 until Day 364. If a subject continues to demonstrate benefit, APL-2 will be administered until Day 729 (Part 2C). Subjects will be assessed by the Investigator every month for Part 2A and Part 2B. Subjects will be assessed by the Investigator at 4 weeks, 8 weeks, and then every 12 weeks until Day 729.

In Cohort 4, if a subject has a sub-optimal clinical response during daily dosing with 270 mg APL-2, the dose may be increased up to 360 mg/day, and doses will be administered at the clinical site every 2 weeks for the first 6 weeks after commencing the higher dose.

For all 4 cohorts the first 4 daily SC doses of APL-2 (from the start of the multiple dose phase for Cohorts 1 and 2 and from Study Day 1 for Cohorts 3 and 4) and subsequent doses on Days 8, 15 and 22 will be administered at the clinical site. In Cohort 4 doses on Days 29, 43, 57, 71, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 421, 477, 533, 617 and 729 will also be administered at the clinical site, as well as up to three additional site visits if individual dose escalation occurs for subjects administered greater than 270mg/day SC APL-2. All other doses will be administered by a trained nurse at the subject's home.

After completion of dosing, subjects will return to the clinical site for additional follow-up visits and the Exit visit.

Originally subjects were not allowed to participate in more than one cohort. PPD With Amendment 4 it was made possible for subjects to participate in more than one cohort.

Following Protocol Amendment 6 Cohort 4 subjects will switch to using an ambulatory syringe pump for delivery of APL-2 and switch from a dextrose to an acetate-buffered mannitol formulation of APL-2 for SC injection.

2.3 Study Sample Size

Cohorts 1-3 will comprise of 2 subjects in each cohort. Cohort 4 will enroll sufficient subjects to ensure at least 6 subjects complete 28 days of dosing with APL-2.

Additional cohorts may be enrolled if it is deemed appropriate by the Sponsor in consultation with the Safety Monitoring Committee (SMC) to repeat a dose level or to study an intermediate dose level.

2.4 Study Flow Chart

Cohorts 1 and 2:

Study Period	Screen	Single Dose							Multiple Dose (Daily)																																Follow up					Exit
Study Month		1							2																																3			4		5
Study Week		1				2	3	4	5							6								7								8									9	10	11	13	15	17
Study Day	-30	1	2	3	4	8	15	22	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	64	71	85	99	113
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
Informed Consent	x																																										
Demographics	x																																									
Medical, transfusion, and thrombosis history	x																																									
Review entry criteria		x																																								
Prescribe preventive antibiotic		x																																								
Physical examination. A	x							x																																	x		x
12-lead electrocardiogram. B	x	x			x	x			x			x				x							x							x											x		x
APL-2 single dose administration. C		S																																								
APL-2 multiple dose administration. C									S	S	S	S	H	H	H	S	H	H	H	H	H	H	S	H	H	H	H	H	H	S	H	H	H	H	H	H						
Injection site assessment. C		x							x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital sign measurements. D	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urinalysis	x	x				x			x							x						x							x								x		x		x	x
Blood. E	x	x	x	x	x	x	x	x	x	x	x	x				x							x							x								x		x			x
Pharmacokinetics. **F**		x	x	x	x	x	x		x	x	x	x											x															x	x	x			x
Anti-APL-2 Ab assay		x				x		x								x							x							x								x	x		x		x
Lactate dehydrogenase		x				x		x															x															x					x
Hematology and chemistry	x	x				x		x															x															x					x
Serology (HIV, HBsAg and HCV)	x																																									
Reticulocyte count		x				x		x															x															x					x
Haptoglobin		x				x		x															x															x					x
Coagulation profile		x						x															x															x					x
Complement profile (C3, CH50 and AP50)		x				x																	x															x					x
Flow cytometry for PNH		x				x																	x															x					x
Flow cytometry C3 deposition		x				x																	x															x					x
Th17/Treg Analysis		x																																				x					x
Free hemoglobin		x				x																	x															x					x
Ferritin, vitamin B12 folate		x				x																	x															x					x
Pregnancy (B-human chorionic gonadotropin)	x							x																																			
Urine pregnancy test. G		x				x			x							x							x							x									x		x		x
FACIT fatigue Scale		x						x															x															x			x		x
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Thrombosis record (MAVE)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

A. A full physical examination will be performed at the scheduled time points indicated. A symptom-driven physical examination may be performed at other times, at the PI's discretion.

B. On dosing visits to be performend wtihin 30 minutes after dosing

C. S = Adminitration at clinical site. H = Administration a patients home. Injection site assessment will be done one hour after study drug administration.

D. On dosing visits to be performend pre- and post-dose. Within 2 hour prior to dosing and wtihin 30 minutes after dosing

E. On dosing visits blood samples will be taken pre-dose. Except Visit 2 PK samples

F. PK samples on Visit 2 will be taken pre-dose and 4 hours post-dose

G. On dosing visits it must be done and read pre-dose

Cohort 3:

Study Period	Screen	Multiple Dose (Daily)																												Follow up					Exit
Study Week	-4	1							2							3							4							5	6	7	9	11	13
Study Day	-30	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	36	43	57	71	85
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
Informed Consent	x																																		
Demographics	x																																		
Medical, transfusion, and thrombosis history	x																																		
Review entry criteria		x																																	
Prescribe preventive antibiotic		x																																	
Physical examination. A	x																													x					x
12-lead electrocardiogram. B	x	x			x				x							x							x							x					x
APL-2 multiple dose administration. C		S	S	S	S	H	H	H	S	H	H	H	H	H	H	S	H	H	H	H	H	H	S	H	H	H	H	H	H						
Injection site assessment. C		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital sign measurements. D	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urinalysis	x	x							x							x							x							x		x		x	x
Blood. E	x	x	x	x	x				x							x							x							x	x	x	x	x	x
Pharmacokinetics. F		x	x	x	x				x							x							x							x	x	x	x	x	x
Anti-APL-2 Ab assay		x							x							x							x							x	x		x		x
Lactate dehydrogenase	x	x							x							x							x							x					x
Hematology and chemistry	x	x							x							x							x							x					x
Serology (HIV, HBsAg and HCV)	x																																		
Reticulocyte count		x							x							x							x							x					x
Haptoglobin		x							x							x							x							x					x
Coagulation profile		x														x														x					x
Complement profile (C3, CH50 and AH50)		x							x							x							x							x					x
Flow cytometry for PNH		x							x							x							x							x					x
Flow cytometry C3 deposition		x							x							x							x							x					x
Th17/Treg Analysis		x																												x					x
Free hemoglobin		x							x							x							x							x					x
Ferritin, vitamin B12 folate		x							x							x							x							x					x
Pregnancy (B-HCG)	x																																		
Urine pregnancy test. G		x							x							x							x								x		x		x
FACIT fatigue Scale		x														x														x			x		x
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Thrombosis record (MAVE)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

A. A full physical examination will be performed at the scheduled time points indicated. A symptom-driven physical examination may be performed at other times, at the PI's discretion.
B. On dosing visits to be performed within 30 minutes after dosing
C. S = Administration at clinical site. H = Administration at patient's home. Injection site assessment will be done one hour after study drug administration.
D. On dosing visits to be performed pre- and post-dose. Within 2 hours prior to dosing and within 30 minutes after dosing
E. On dosing visits blood samples will be taken pre-dose (except Visit 2 where samples will be collected pre-dose in addition to a post-dose PK sample)
F. PK samples on Visit 2 will be taken pre-dose and 4 hours post-dose
G. On dosing visits it must be done and read pre-dose

Cohort 4:

Study Period	Screen	PART 1 - Multiple Dose (Daily)																											
Study Week	-4	1							2							3							4						
Study Day	-30	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Informed Consent	X																												
Demographics	X																												
Medical, transfusion, and thrombosis history	X																												
Review entry criteria		X																											
Vaccination. A	X																												
Preventive antibiotic. B		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination. C	X																												
12-lead electrocardiogram. D	X	X			X				X							X							X						
APL-2 administration. E		S	S	S	S	H	H	H	S	H	H	H	H	H	H	S	H	H	H	H	H	H	S	H	H	H	H	H	H
Injection site assessment. F		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital sign measurements. G	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X							X							X							X						
Blood. I	X	X	X	X	X				X							X							X						
Pharmacokinetics. I		X	X	X	X				X							X							X						
Anti-APL-2 Ab assay		X							X							X							X						
Lactate dehydrogenase	X	X							X							X							X						
Hematology and chemistry.	X	X							X							X							X						
Serology (HIV, HBsAg and HCV). J	X																												
Reticulocyte count		X							X							X							X						
Haptoglobin		X							X							X							X						
Coagulation profile		X														X													
Complement profile (C3, CH50 and AH50)		X							X							X							X						
Flow cytometry for PNH		X							X							X							X						
Flow cytometry C3 deposition		X							X							X							X						
Th17/Treg Analysis		X																											
Free hemoglobin		X							X							X							X						
Ferritin, vitamin B12 folate		X							X							X							X						
Pregnancy (B-HCG)	X																												
Urine pregnancy test. K		X							X							X							X						
FACIT fatigue Scale		X														X													
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Thrombosis record (MAVE). L		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

See Study Flow Chart Footnotes below continuation flow chart

Study Period	Part 2A - Treatment (Daily from Day 29 to Day 84)								
Study Week	5		6	7 and 8		9 and 10		11 and 12	
Study Day	29	30 to 35	36 to 42	43	44 to 56	57	58 to 70	71	72 to 84
Study Visit	30	31 to 36	37 to 43	44	45 to 57	58	59 to 71	72	73 to 85
Informed Consent									
Demographics									
Medical, transfusion, and thrombosis history									
Review entry criteria									
Preventive antibiotic. B	X	X	X	X	X	X	X	X	X
Physical examination. C	X					X			
12-lead electrocardiogram. D	X			X		X		X	
APL-2 administration. E	**S**	**H**	**H**	**S**	**H**	**S**	**H**	**S**	**H**
Injection site assessment. F	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Vital sign measurements. G	X	X	X	X	X	X	X	X	X
Urinalysis	X			X		X		X	
Blood. I	X			X		X		X	
Pharmacokinetics. I	X			X		X		X	
Anti-APL-2 Ab assay	X							X	
Lactate dehydrogenase	X			X		X		X	
Hematology and chemistry.	X			X		X		X	
Reticulocyte count	X			X		X		X	
Haptoglobin	X			X		X		X	
Coagulation profile	X			X		X		X	
Complement profile (C3, CH50 and AP50)	X			X		X		X	
Flow cytometry for PNH/C3 deposition	X			X		X		X	
Th17/Treg Analysis	X								
Free Hemoglobin	X			X		X		X	
Ferritin, vitamin B12 folate	X			X		X		X	
Urine pregnancy test. K	X			X		X		X	
FACIT fatigue Scale	X			X				X	
Adverse events	X	X	X	X	X	X	X	X	X
Thrombosis record (MAVE) L	X	X	X	X	X	X	X	X	X

See Study Flow Chart Footnotes below continuation flow chart

Study Period	Part 2 B- Treatment (Daily from Day 85 to Day 364) - continued... M											
Study Week	13 to 16		17 to 20		21 to 24		25 to 28		29 to 32		33 to 36	
Study Day	85	86 to 112	113	114 to 140	141	142 to 168	169	170 to 196	197	198 to 224	225	226 to 252
Study Visit	86	87 to 113	114	115 to 141	142	143 to 169	170	171 to 197	198	199 to 225	226	227 to 253
Informed Consent												
Demographics												
Medical, transfusion, and thrombosis history												
Review entry criteria												
Preventive antibiotic. B	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination. C	X											
12-lead electrocardiogram. D	X		X		X		X		X		X	
APL-2 administration. E	S	H	S	H	S	H	S	H	S	H	S	H
Injection site assessment. F	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Vital sign measurements. G	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X		X		X		X		X		X	
Blood. I	X		X		X		X		X		X	
Pharmacokinetics. I	X		X		X		X		X		X	
Anti-APL-2 Ab assay	X				X				X			
Lactate dehydrogenase	X		X		X		X		X		X	
Hematology and chemistry.	X		X		X		X		X		X	
Coagulation profile	X		X		X		X		X		X	
Reticulocyte count	X		X		X		X		X		X	
Haptoglobin	X		X		X		X		X		X	
Complement profile (C3, CH50 and AP50)	X		X		X		X		X		X	
Flow cytometry for PNH/C3 deposition	X		X		X		X		X		X	
Th17/Treg Analysis	X											
Free Hemoglobin	X		X		X		X		X		X	
Ferritin, vitamin B12 folate	X		X		X		X		X		X	
Urine pregnancy test. K	X		X		X		X		X		X	
FACIT fatigue Scale	X				X				X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Thrombosis record (MAVE) L	X	X	X	X	X	X	X	X	X	X	X	X

See Study Flow Chart Footnotes below continuation flow chart

Study Period	... continued - Part 2B - Treatment (Daily from Day 85 to Day 364) M							
Study Week	37 to 40		41 to 44		45 to 48		49 to 52	
Study Day	253	254 to 280	281	282 to 308	309	310 to 336	337	338 to 364
Study Visit	254	255 to 281	282	283 to 309	310	311 to 337	338	339 to 365
Informed Consent								
Demographics								
Medical, transfusion, and thrombosis history								
Review entry criteria								
Preventive antibiotic. B	X	X	X	X	X	X	X	X
Physical examination. C	X							
12-lead electrocardiogram. D	X		X		X		X	
APL-2 administration. E	**S**	**H**	**S**	**H**	**S**	**H**	**S**	**H**
Injection site assessment. F	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Vital sign measurements. G	X	X	X	X	X	X	X	X
Urinalysis	X		X		X		X	
Blood. I	X		X		X		X	
Pharmacokinetics. I	X		X		X		X	
Anti-APL-2 Ab assay	X				X			
Lactate dehydrogenase	X		X		X		X	
Hematology and chemistry.	X		X		X		X	
Coagulation profile	X		X		X		X	
Reticulocyte count	X		X		X		X	
Haptoglobin	X		X		X		X	
Complement profile (C3, CH50 and AP50)	X		X		X		X	
Flow cytometry for PNH/C3 deposition	X		X		X		X	
Th17/Treg Analysis	X							
Free Hemoglobin	X		X		X		X	
Ferritin, vitamin B12 folate	X		X		X		X	
Urine pregnancy test. K	X		X		X		X	
FACIT fatigue Scale	X				X			
Adverse events	X	X	X	X	X	X	X	X
Thrombosis record (MAVE) L	X	X	X	X	X	X	X	X

Study Period		... continued - Part 2C - Treatment (Daily from Day 365 to Day 729) M						Part 3 – Follow-up and Exit or ET (N)		
	Study Week	53	61	69	81	93	105	107	109	113
	Study Day	365 (+/-7 days)	421 (+/-7 days)	477 (+/-7 days)	561 (+/-14 days)	645 (+/-14 days)	729 (+/-14 days)	743 (+/- 3 days)	757 (+/- 3 days)	785 (+/- 7 days)
	Study Visit	366	367	368	369	370	371	372	373	374
Informed Consent										
Demographics										
Medical, transfusion, and thrombosis history										
Review entry criteria										
Preventive antibiotic. B		X	X	X	X	X	X			
Physical examination. C		X						X	X	X
12-lead electrocardiogram. D		X	X	X	X	X	X	X	X	X
APL-2 administration. E		S	S	S	S	S	S			
Injection site assessment. F		X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X
Vital sign measurements. G		X	X	X	X	X	X	X	X	X
Urinalysis		X	X	X	X	X	X	X	X	X
Blood. I		X	X	X	X	X	X	X	X	X
Pharmacokinetics. I		X	X	X	X	X	X	X	X	X
Anti-APL-2 Ab assay		X	X	X	X	X	X	X	X	X
Lactate dehydrogenase		X	X	X	X	X	X	X	X	X
Hematology and chemistry.		X	X	X	X	X	X	X	X	X
Coagulation profile		X	X	X	X	X	X	X	X	X
Reticulocyte count		X	X	X	X	X	X	X	X	X
Haptoglobin		X	X	X	X	X	X	X	X	X
Complement profile (C3, CH50 and AP50)		X	X	X	X	X	X	X	X	X
Flow cytometry for PNH/C3 deposition		X	X	X	X	X	X	X	X	X
Th17/Treg Analysis		X			X		X	X	X	X
Free Hemoglobin		X	X	X	X	X	X	X	X	X
Ferritin, vitamin B12 folate		X	X	X	X	X	X	X	X	X
Urine pregnancy test. K		X	X	X	X	X	X	X	X	X
FACIT fatigue Scale		X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X
Thrombosis record (MAVE) L		X	X	X	X	X	X	X	X	X

See Study Flow Chart Footnotes on next page

A. If Neisseria meningitidis vaccine/s are administered during screening (up to Day –14), a booster (for both vaccinations) should be administered after 2 months. If Pneumococcal vaccination is required during screening, a dose of PCV13 will be administered at least two weeks prior to Day 1 and a dose of PPSV23 will be administered at least 8 weeks later.

B. Preventive antibiotics will be prescribed prior to Visit 2. Antibiotics will be taken from Visit 2 until 14 days after the last dose of APL-2.

C. Full physical examination will be performed at the scheduled time points indicated. A symptom-driven physical examination may be performed at other times, at the PI's discretion.

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

E. S = Administration at clinical site. H = Administration at subject's home. Treatment may be stopped at any time if the investigator and sponsor conclude that there is no demonstration of clinical benefit to APL-2 to continue administration. Subjects may self-administer the SC infusions at home, after receiving appropriate training by a research nurse or other personnel.

F. Injection site assessment will be performed within 30 minutes after APL-2 administration. After the subjects start to self-administer APL-2 via the pump, injection site reactions will no longer be evaluated by research personnel after at-home administrations. Subjects will be instructed to report any injection site reaction to the study coordinator.

G. If done on a dosing day, vital signs will be measured within 2 hours prior to dosing and within 30 minutes after dosing. If the subjects start to self-administer APL-2 via the pump, vital signs will no longer be measured before and after at-home administrations.

H. Reserved – See note E.

I. If done on a dosing day, blood samples will be taken pre-dose with the exception that at Visit 2 only a pharmacokinetic sample will be taken pre-dose and at 4 hours post-dose.

J. Absence of Human immunodeficiency virus, Hepatitis B surface antigen, and Hepatitis C virus, will be confirmed prior to APL-2 administration.

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

L. MAVE = Major Adverse Vascular Event. After the subjects start to self-administer APL-2 via the pump, MAVE will no longer be evaluated by research personnel during home visits. Subjects will be instructed to report any events to the study coordinator.

M. If the dose is increased to >270 mg/day, the subject will attend the clinical site for safety visits every 2 weeks (instead of every 4 weeks) for the first 6 weeks after the dose increase i.e. up to an additional 3 clinic visits. The extra clinic visits will be recorded as Unscheduled Visits and will alternate with the scheduled monthly visits.

N. Subjects that discontinue dosing at any time during part 1, 2A, 2B or 2C, will move directly into Part 3 for the exit or early termination visit.

3.0 GENERAL ANALYSIS DEFINITON

3.1 General Considerations and Definitions of Baselines

No formal statistical testing will be performed on data from Cohorts 1-3. Comparisons to baseline will be performed for Cohort 4.

Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. With so few subjects in Cohorts 1-3, continuous data, unless specifically mentioned otherwise, will only be summarized for Cohort 4.

Categorical data will be summarized by treatment group and over all subjects using frequency tables. The summary over all subjects will be based on unique subjects, so subjects who participate in more than one cohort will only be counted once.

The baseline for this study will be taken as the 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).

With Cohorts 1 and 2 including a single dose phase before the multiple dose phase and Cohorts 3 and 4 only including a multiple dose phase, data from Cohorts 1 and 2 will be presented for the single dose phase separately from the multiple dose phase.

Where multiple dose phase data from Cohorts 1-4 are presented together, changes from baseline will use the last measurement prior to the start of multiple dosing as baseline. For Cohorts 3 and 4 baseline is scheduled to be Day 1, whilst for Cohorts 1 and 2 the multiple dose baseline may be Day 1 (ECG, complement profile, and cytometry data), Day 22 (FACIT and laboratory safety test data), or Day 29 (vital sign data).

For Cohort 4 the treatment phase consists of four parts - Part 1 covers the first 28 days of dosing and Parts 2A, 2B and 2C cover the treatment period till Day 84, Day 364 and Day 729 respectively. To assist in the reporting of the study the treatment phases for Cohorts 1-3 will also be considered as Part 1, as this will cover the dosing period till the end of 28 days multiple dosing.

All collected data will be listed. Data listings will be presented by cohort. Subjects who enter more than one cohort will be identified in the listings using a unique flag, so it is possible to link the data across cohorts. For Cohort 4, a dose column will be added to all listings that contain post-dose assessments, where the last dose that was taken before the assessment will be listed.

Listings will include study days, which are relative to the first day of dosing (Day 1). For subjects who participate in more than one cohort the study day for each cohort will be relative to the first day of dosing in that cohort.

Study days will be calculated as:

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

$$\text{Study Day} = \text{visit date} - \text{date of first APL-2 dose} + 1$$

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

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

Where assessments/events occur after the start of the multiple dose phase for Cohorts 1 and 2, the listings will also include the study days relative to the first day of the multiple dose phase (henceforth referred to as the 'multiple dose day').

3.2 Handling of Missing Data

3.2.1 Safety Data

Missing safety data (e.g. partial dates and missing severities) will be dealt with on a case by case basis if they arise. As a general rule, a conservative approach will be adopted (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).

Handling of missing dates/times are detailed in the appropriate sections.

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

The original data will always be presented in the listings.

3.2.2 PK and 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 the following thereafter:

- missing for the calculation of PK parameters
- zero in linear plots
- LLOQ for semi-logarithmic plots

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

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.

4.0 STUDY SUBJECTS

4.1 Dispositions of Subjects

The number of subjects screened and the number of subjects participating in more than one cohort will be presented over all subjects.

The following numbers of subjects will be presented for each cohort:

For Cohorts 1 and 2:

- who receive the single dose
- who withdraw prior to Day 22 (i.e. prior to multiple dosing)

For All Cohorts (unless otherwise specified):

- who receive at least one dose during multiple dose phase
- who complete Part 1
- who withdraw during multiple dose phase of Part 1
- who receive at least one dose during Part 2A (Cohort 4 only)
- who complete Part 2A (Cohort 4 only)
- who withdraw during Part 2A (Cohort 4 only)
- who receive at least one dose during Part 2B (Cohort 4 only)
- who complete Part 2B (Cohort 4 only)
- who withdraw during Part 2B (Cohort 4 only)
- who receive at least one dose during Part 2C (Cohort 4 only)
- who complete Part 2C (Cohort 4 only)
- who withdraw during Part 2C (Cohort 4 only)
- who complete the study (i.e. through to end of study follow-up)
- who withdraw during follow-up and reason for withdrawal
- in each analysis set
- who are still on study (interim analysis only)

Reasons for discontinuation and screen failures will also be summarized.

4.2 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedure defined in the protocol. A subset of the protocol deviations may be identified as a major protocol deviation as described below:

Important Protocol Deviation: An important protocol deviation 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.

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 (including details of the deviation)

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 error
5. Pharmacy error
6. Laboratory error
7. Investigator/staff decision
8. Other

Upon soft lock of the database, all documented protocol deviations in the study will be reviewed to identify all important protocol deviations. The data review team will include representatives from clinical operations, medical, data management, and statistics. Final decisions will be documented and databased in the SAS analysis datasets. Number and proportion of subjects with protocol deviations (Important/Other) may also be tabulated by protocol deviation category if data warrants. Subjects excluded from each analysis set will be tabulated with reason for exclusion.

4.3 Analysis Datasets

4.3.1 Screened Set

The Screened Set will include all patients 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 subject disposition.

4.3.2 Intention to Treat (ITT) and Safety Sets

The ITT and Safety Sets will include all subjects enrolled who receive at least one dose of the study medication.

4.3.3 PK and PD Sets

The PK set will include all subjects in the Safety Set who have at least one PK sample drawn with a measurable serum concentration of study drug. The PD set will include all subjects in the Safety Set who have at least one PD sample drawn and a measurable PD value.

5.0 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic data, medical history, concomitant disease and prior medication will be summarized by cohort and for the overall study by means of descriptive statistics (n, mean, SD, median, minimum and maximum) or frequencies (counts and percentages).

Time since diagnosis of PNH (years) and the baseline measurements for complement parameters (CH50, AP50 and C3), clonal distribution of PNH Red Blood Cells (RBC), hemoglobin level, LDH, haptoglobin, reticulocyte count, total bilirubin and total FACIT score will be summarized by cohort and overall using summary statistics for continuous variables. In addition, the number of transfusions in the last 12 months prior to randomization will be summarized using summary statistics of median, minimum and maximum.

Time since diagnosis = (informed consent date - date of diagnosis + 1)/365.25

Medical history, concomitant disease and prior medications will also be summarized for each dose group (cohort) and over all subjects by MedDRA Version 17.0 System Organ Class (SOC) and Preferred Term (PT). 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 WHO ATC Class 1 Term and WHO drug Preferred Term (March 2014).

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

Subjects who participate in more than one cohort will only be counted once in the summaries over all subjects, using the data collected for their first cohort. The summaries by cohort will use baseline data from each of the cohorts.

6.0 CONCOMITANT MEDICATION

Concomitant medications will include any medications being taken after the subject starts their study medication. Hence, medications ongoing at the start of dosing will be counted in both the prior and concomitant medication summaries.

Concomitant medications will be summarized for each dose group (cohort) and overall for subjects in the Safety Set. Concomitant medications will be summarized by WHO ATC Class 1 Term and WHO drug Preferred Term (March 2014).

Subjects who participate in more than one cohort will only be counted once in the overall summary, all concomitant medications across the cohorts will be included in the overall summary.

A separate listing will provide information on the eculizumab dosing regimen. The listing will detail the subject's periods of each dosing regimen. Hence if the subject stays on the same dosing regimen during the study there will be a single entry in the listing with the study start and stop dates and dose.

If either the start or stop date of medication is missing, the worst or most conservative

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

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

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

7.0 TREATMENT EXPOSURE AND TREATMENT COMPLIANCE

Treatment compliance will be calculated based on the drug accountability log documented by the site staff.

For each subject the following will be listed:

- For Cohorts 1 and 2, the last phase of dosing (single or multiple)
- Last study day of dosing within the last study phase (i.e. Study Day calculated from Day 1 if last day is in the single dose phase in Cohorts 1 and 2, or the last dose day relative to the start of multiple dosing)
- Number of days during the multiple dose phase they received treatment
- Compliance (percentage of days they took medication prior to study discontinuation/completion).

For Cohort 4 the number of days dosed and the compliance will be presented for Parts 1, 2A, 2B and 2C separately as well as over the whole study.

Where subjects in Cohort 4 have their dose escalated to 360mg/day separate information will be supplied for each dose. This will also be done if subjects change their dose for any other reason, with rows of the listing being in chronological order.

For those subjects who switch to using the ambulatory syringe pump the first day of using the pump will be listed. The date of change in formulation will also be listed.

8.0 EFFICACY ANALYSIS

8.1 Exploratory Efficacy Analysis

RBC Transfusions

The absolute and change in number of RBC transfusions per month and the absolute and change number of units transfused per month will be summarized by cohort and by phase of the study (Parts 1, 2A, 2B, 2C and 3) and over the whole on-treatment study parts (Parts 1, 2A, 2B and 2C). For Cohorts 1 and 2 the data will be split by the single and multiple dose phases.

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 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 unit transfused per month.

The baseline number of transfusions per month will be calculated as number of transfusions reported on 12-month transfusion history /12. For subjects who enter both cohorts the baseline for both cohorts will be taken from the 12-month transfusion history prior to their first cohort.

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.

FACIT

The Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale (Version 4) is an exploratory efficacy endpoint. The individual fatigue score will be calculated (see Appendix 1 of the protocol), where a higher score corresponds to a higher quality of life.

Individual fatigue scores will be tabulated along with changes from baseline for the ITT population by cohort, study part and study day.

As mentioned in Section 3.1 the multiple dose phase data from Cohorts 1-4 will be listed with changes from baseline using the last measurement before the start of multiple dosing as baseline (scheduled as Day 22 for Cohorts 1 and 2 and Day 1 for Cohorts 3 and 4). Additionally, Cohort 1 and 2 data from both single and multiple dose phases will be listed using Study Day 1 as baseline for the changes from baseline.

In addition to the observed values and changes from baseline, the listing will also include the study day of assessment and the multiple dose day for assessments made during the multiple dose phase.

For Cohort 4, the absolute values and changes from baseline will be summarized, using descriptive statistics, by study visit. The associated 95% confidence interval and 2-sided p-value (Student's t-test) for the changes from baseline will also be presented.

Total score and changes from baseline in individuals' fatigue scores will be plotted by multiple dose day, with each cohort (dose) and each subject being identifiable. For both the total score and changes from baseline, two plots will be presented. The first will present the Part 1 data (multiple dose data only for Cohorts 1 and 2) and the

follow-up data for Cohorts 1-3. The follow-up data for Cohort 4 will also be included if the subject doesn't continue dosing into Part 2A. Subjects who participate in more than one cohort will be identified in a footnote.

The second plot will present the Cohort 4 data over the whole study.

For all plots a dotted line will be used to identify follow-up data and the actual sampling day will be used on the x-axis.

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

9.0 SAFETY ANALYSIS

9.1 Adverse Events

Treatment emergent adverse events (TEAE) are defined as those AEs that develop or worsen after the first dose of study medication, up to 30 days beyond the last dose of study medication. Version 17.0 of Medical Dictionary for Regulatory Activities (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 Summary

A by-subject TEAE data listing, 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 and stop days (relative to the first dosing day), onset time since last dose, and the duration of AEs will be included in listings.

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

- Local or systemic infection of any origin
- Clinically significant decrease in kidney function
- Thrombosis
- Injection site reactions
- Infusion pump related events

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 Oracle Remote Data Capture (RDC) 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.

For Cohorts 1 and 2, AEs emergent during the single dose phase will be tabulated separately to those during the multiple dose phase, and those during the multiple dose phase will be presented along with Cohorts 3 and 4. For Cohort 4 TEAEs will be tabulated separately for Parts 1 and 2.

A topline summary will present the number of subjects by cohort (dose) and overall with:

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

- TEAEs by SOC and preferred term in descending order of total events
- TEAEs by preferred term in descending order of total events
- TEAEs regarded as at least possibly related to study drug by SOC and preferred term
- TEAEs and Serious AEs by maximum severity, and by SOC and preferred term
- TE AESIs by maximum severity

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

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 Part 1 will be categorized under Part 1 even if it continues into Part 2A (unless it increases in severity). Summaries will be ordered by descending order of event count in the overall column (firstly the SOCs will be ordered and then the preferred terms within each SOC).

If a subject is enrolled into more than one cohort, they will be counted in each cohort separately, but only once in the overall column for each preferred term.

9.2 Laboratory Parameters

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, and Urinalysis results will be presented separately.

As mentioned in Section 3.1 the multiple dose phase data from Cohorts 1-4 will be listed with changes from baseline using the last measurement before the start of multiple dosing as baseline (scheduled as Day 22 for Cohorts 1 and 2 and Day 1 for Cohorts 3 and 4). Additionally, Cohort 1 and 2 data from both single and multiple dose phases will be listed using Study Day 1 as baseline for the changes from baseline.

Listings of out of range lab results with their corresponding changes from baseline will be presented for the single dose phase (for Cohorts 1 and 2 with a baseline of Study Day 1) and for the multiple dose phase. For Cohort 4 the presentations will identify if the results were from Parts 1, 2A, 2B or 2C.

9.3 Vital Signs

The listing of vital sign data will include change from baselines. As mentioned in Section 3.1 the multiple dose phase data from Cohorts 1-4 will be listed with changes from baseline using the last measurement before the start of multiple dosing as baseline (scheduled as Day 29 for Cohorts 1 and 2 and Day 1 for Cohorts 3 and 4). Additionally Cohort 1 and 2 data from both single and multiple dose phases will be listed using Study Day 1 as baseline for the changes from baseline.

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 (^{o}C)		≥ 38

The number of subjects satisfying each of the above criteria will also be summarized for the safety population by cohort (dose) and study part. As some of the parameters

have both low and high criteria it is possible for a subject to meet both over the reporting period. Consequently, for these parameters, the number of subjects will be presented in the following mutually exclusive categories:

- All values in normal range
- ≥1 abnormally low reading and no abnormally high reading
- ≥1 abnormally high reading and no abnormally low reading
- ≥1 abnormally low and ≥1 abnormally high reading

For Cohorts 1 and 2 the data will be split by the single and multiple dose phases.

9.4 Electrocardiograms

The listing of ECG data will include change from baselines. As mentioned in Section 3.1 the multiple dose phase data from Cohorts 1-4 will be listed with changes from baseline using the last measurement before dosing as baseline (Day 1 for all cohorts).

In the listing, data fulfilling the following criteria will be flagged:

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

ECG results will be classified as normal or abnormal, with the abnormal further classified as either not clinically significant (NCS) or clinically significant (CS). This information will be included in listings.

The number of subjects satisfying each of the above criteria will also be summarized for the safety population by cohort (dose) and study part. For Cohorts 1 and 2 the data will be split by the single and multiple dose phases. As some of the parameters have both low and high criteria it is possible for a subject to meet both over the reporting period. Consequently, for these parameters, the number of subjects will be presented in the following mutually exclusive categories:

- All values in normal range
- ≥1 abnormally low reading and no abnormally high reading
- ≥1 abnormally high reading and no abnormally low reading
- ≥1 abnormally low and ≥1 abnormally high reading

9.5 Antigenicity Analysis

These data will be listed by cohort.

10.0 PHARMACOKINETIC ANALYSES

PK Concentrations

To assess the plasma concentration profile of APL-2 after both single and multiple doses (steady state), concentrations will be listed and plotted.

Presentations will include:

- For Cohorts 1 and 2, a listing of all concentrations sorted by dose group (cohort), subject number, study day, and nominal time post dose will be presented for the single dose phase. For all cohorts (1-4) a separate listing of all concentrations sorted by dose group (cohort), subject number, multiple dose day, and nominal time post dose will be presented for the multiple dose phases. The actual time will also be listed, along with the deviations from nominal time in each of these listings.
- For Cohort 4, APL-2 concentrations will be summarized by study visit using descriptive statistics. The number of subjects with a value BLQ will also be tabulated.
- Linear and log-linear individual concentration profile plots against actual time (with each cohort [dose] being identifiable).
    - For Cohorts 1 and 2 a plot will be presented for Study Days 1 to 29 (all concentrations following the single dose but recorded before the first dose of multiple dosing).
    - For Cohorts 1-4, a plot will be presented for Multiple Dose Days 1 to 29 (the last concentration before the start of multiple dosing through to the last concentration no more than 1 day after the Day 29 dose).
    - For Cohort 4, a plot will be presented over the whole study.

Subjects who participate in more than one cohort will be identified in footnotes.

For individual subject plots by time, the actual PK sampling time will be used.

PK Parameters

For Cohorts 1 and 2 only, the following PK parameters for APL-2 will be derived from the 'single dose' individual serum concentrations-time data, using actual sample times:

AUC_{0-t} The area under the serum concentration versus time curve, from time 0 to the last measurable concentration prior to the start of multiple dosing*, as calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing.

C_{max} Maximum observed serum concentration.

T_{max}	Time of the maximum measured serum concentration. If the maximum value occurs at more than one time point, t_{max} is defined as the first time point with this value.

**Until the pre-dose concentration on Day 29. If a subject starts multiple dosing after Day 29 then a footnote will indicate the study day of their last single dose blood sample.*

With too few samples taken during the terminal phase of the concentration profile to reliably determine the elimination rate constant $t_{1/2}$, $AUC_{0\text{-}inf}$, CL/F and V_z/F will be estimated from the population PK model.

For the multiple dose phase the APL-2 parameters AUC_{total} and $C_{trough,max}$ will be estimated for the individual serum concentration data, using a non-compartmental approach. AUC_{total} will be calculated using the linear-log trapezoidal method. It will be determined using all concentrations measured from the last dose till the last quantifiable concentration. For Cohort 4, $C_{trough,max}$ will be calculated for both 270mg and 360mg where subjects receive both doses.

PK parameters will be listed by cohort. For Cohort 4, PK parameters will be summarized using descriptive statistics. Geometric mean and CV will also be presented. Additional analyses will be performed as deemed necessary upon review of the data.

Population PK Modelling

In addition to the above analyses, all PK plasma concentration data will be used to update and further develop the population PK model which is currently based on the PK data collected in studies APL-CP0713-1 and APL-CP1014. The methods and procedures that will be used as well as the scope of the work that will be undertaken will be presented in a Population PK Analysis Plan.

11.0 PHARMACODYNAMIC ANALYSIS

PD parameters include the following:

1. Lactate Dehydrogenase (LDH),
2. Reticulocyte count,
3. Haptoglobin,
4. Hemoglobin level,
5. Total bilirubin, and
6. Serum levels of complement parameters (CH50, AH50, and C3)

These data will be listed by cohort, study part and subject along with changes from baseline and percent changes from baseline. As mentioned in Section 3.1 the multiple dose phase data from Cohorts 1-4 will be listed with changes and percentage changes from baseline using the last measurement before the start of multiple dosing as

baseline (PD parameters 1-5: scheduled as Day 22 for Cohorts 1 and 2 and Day 1 for Cohorts 3 and 4; PD parameter 6: Day 1 for all cohorts). Additionally, Cohort 1 and 2 data from both single and multiple dose phases will be listed using Study Day 1 as baseline for the changes and percentage changes from baseline.

For Cohort 4, absolute values, changes from baseline and percentage changes from baseline will be summarized, using descriptive statistics, by study visit. The associated 95% confidence interval and 2-sided p-value (Student's t-test) for the changes from baseline will also be presented.

For LDH, reticulocyte count, haptoglobin and total bilirubin the number and percentage of subjects ≤ ULN and ≤ 1.5*ULN will also be summarized by study visit for Cohort 4 only. Plots, paged by subject, will include these parameters and present the value related to ULN (i.e. value/ULN) against time. Each parameter will have a different symbol and a legend to identify the parameters will be included. A vertical line, labelled with the dose, will be added to the plot to identify any dose change during the study.

For hemoglobin level the number and percentage of subjects ≥ LLN will also be summarized by study visit for Cohort 4 only.

For each of the above parameters (except CH50 and AH50), individual values, changes from baseline, and percent changes from baseline will be plotted against actual study day (with each cohort and subject being identifiable) for the multiple dose phase. For CH50 only individual values and change from baseline will be plotted. AH50 will not be plotted as AH50 should be completely inhibited (i.e. BLQ) for subjects receiving Soliris®. For each of the individual value, changes from baseline, and percentage changes from baseline endpoints, three plots will be presented.

The first will present individual values, changes from baseline, and percentage changes from baseline over the study (single and multiple dose phases) plotted against assessment for Cohorts 1 and 2 using the last measurement before the start of dosing (scheduled as Day 1) as baseline.

The second will present the Part 1 data (multiple dose data only for Cohorts 1 and 2) and the follow-up data for Cohorts 1-3. The follow-up data for Cohort 4 will also be included if the subject doesn't continue dosing into Part 2A. Subjects who participate in more than one cohort will be identified in a footnote.

The third will present the Cohort 4 data over the whole study.

For all plots a dotted line will be used to identify follow-up data and the actual sampling day will be used on the x-axis.

PD parameters also include the following:

- PNH granulocytes (percent FLAER), and

- PNH monocytes (percent FLAER)
- C3 deposition on RBCs (percent C3d CD59 Type I, II, III and II+III*)
- clonal distribution of PNH RBCs (percent CD59 Type I, II, III and II+III**)

**C3d deposition on RBC cells (percent Type II + III) is the number of events for C3d deposition on RBC cells (Type II) plus number of events for C3d deposition on RBC cells (Type III) divided by number of events for PNH CD59 Type II and III expressed as a percent.*

*** Clonal distribution of PNH RBCs (percent Type II + III) is the sum of the clonal distribution of PNH RBCs Type II and Type III.*

For Cohort 4, absolute values and changes from baseline will be summarized, using descriptive statistics, by study visit.

The individual PNH granulocytes (percent FLAER) and the change from baseline (Day 1 for all cohorts) will be plotted by study day with each subject and cohort and subject being identifiable. The first plot will present the Part 1 data (multiple dose data only for Cohorts 1 and 2) and the follow-up data for Cohorts 1-3. The follow-up data for Cohort 4 will also be included if the subject doesn't continue dosing into Part 2A. Subjects who participate in more than one cohort will be identified in a footnote. A second plot will present the Cohort 4 data over the whole study. A dotted line will be used to identify follow-up (Part 3). The actual sampling day will be used on the x-axis. These plots will be repeated for PNH monocytes (percent FLAER) individual and change from baseline values.

Individual subject plots of the percentage distribution will be presented for the C3 deposition on RBC cells parameters, with all parameters included on the same subject plot. The first plot will present the Part 1 data (multiple dose data only for Cohorts 1 and 2) and the follow-up data for Cohorts 1-3. The follow-up data for Cohort 4 will also be included if the subject doesn't continue dosing into Part 2A. Subjects who participate in more than one cohort will be identified in a footnote. A second plot will present the Cohort 4 data over the whole study. A dotted line will be used to identify follow-up (Part 3). The actual sampling day will be used on the x-axis. This plot will be repeated for clonal distribution of PNH RBCs parameters.

Clonal distribution of PNH RBCs (percent Type II + III) over time will be plotted by cohort with each subject being identifiable. Subjects who enter both cohorts will be identified in a footnote. Separate plots will be presented for Part 1 (all cohorts, multiple dose phase only for Cohorts 1 and 2) and Cohort 4 (whole study). A dotted line will be used to identify follow-up (Part 3). The actual sampling day will be used on the x-axis. These plots will be repeated for Clonal distribution of PNH RBCs (percent Type III), C3d deposition on RBC cells (percent Type II + III) and C3d deposition on RBC cells (percent Type III).

Listings of the T-helper 17 (Th17) and T-regulatory (Treg) cell analysis will be prepared for the single dose phase and the multiple dose phase. The analysis will be

performed by the Research Lab in Renal Medicine at the Icahn School of Medicine at Mount Sinai Medical School in New York City.

12.0 INTERIM ANALYSIS

An external, independent Safety Monitoring Committee (SMC) will regularly review cumulative safety/tolerability, PK and PD data during the dose escalation phase of the study. The first SMC assessment will occur before the initiation of Cohort 2. Following this, assessments will occur approximately every four weeks. A key responsibility of the SMC will be to make recommendations to continue, modify, or stop dose escalation (or the study) based on current safety data, particularly the AEs of special interest listed in Section 9.1.

Additional safety reviews will be scheduled as recommended by the SMC or the sponsor. At the Sponsor's request, safety tables, figures, and data listings may be presented to the sponsor's consultants for the purposes of planning the next Phase 1 or initial Phase 2 studies prior to database lock. These interim analyses will be performed on data that will be edit-checked and monitored.

Preliminary PK analysis may be performed to evaluate the sampling time points as the study progresses and to guide the dose escalation decision.

When all subjects have completed (or discontinued) Part 2A in Cohort 4 the data collected up to and including these study visits will be reported. Further reports may be prepared with each report containing cumulative information. These reports will be performed on data that will have been fully checked and considered as final. Any changes to the data previously reported will be fully auditable and discussed in the subsequent reports.

13.0 SOFTWARE AND PROGRAMMING SPECIFICATIONS

13.1 Statistical Software

All statistical programs will be written in SAS® version 9.3. CCI

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

13.2 Generating Programming Specifications

Appendix 1 provides a list of all the TLFs that are planned to be produced.

13.2.1 Formatting Specifications

The following formatting specifications will be used to output TLFs:

- TLFs are outputted by SAS Output Delivery System (ODS) into Rich Text Files (RTF) and Portable Document Format (PDF) formats.
  - Tables and Listings will include borders around all headings and data cells.
  - Output will be in landscape orientation with margins of 1.5 inches on top, and 1 inch for right, left, and bottom.
  - The default font to be in tables/listings/figures will be Times New Roman or Courier New.
  - Preferred and minimum font size:

Portion of Output	Preferred	Minimum
Page Header	12 pt	8 pt
Title	12 pt bold	8 pt
Column header	12 pt bold	8 pt
Cells	9 pt	8 pt
Footnote	8 pt bold	8 pt
Page Footer	12 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.

13.2.2 Standard Text Specifications

13.2.2.1 Header

All output (table, listing, or figure) will have the following header at the upper left corner:

Apellis Pharmaceuticals, Inc.
Protocol: APL-CP0514
Clinical Study Report

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

13.2.2.2 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 population descriptor.

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

Table 14.1.1.1
Disposition of Subjects
Screened Set

13.2.2.3 Footnotes

Unless otherwise specified, footnotes will appear on all pages within the tables and listings.

- 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, Min = Minimum, Max = Maximum.

- Each line of a complete footnote should end with a period.
- When an abbreviation (e.g. AE, SAE, ITT, etc.) appears in the whole set of TLFs for a study, a footnote should be provided.
- 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 related directly to the displayed content of a table/listing/figure.
- Footnotes will not contain detailed/technical elaboration of, for example, a mathematical/statistical formula, a statistical term/test, or an algorithm for deriving a parameter value, which should be addressed in the text of the SAP.
- All footnotes will be at the lowest line of the page immediately above the footer. There will be one space between the last footnote and the footer.
- For Tables, the first footnote will provide source listings and/or analysis datasets names for cross-referencing.
- Any use of the FACIT score must include the footnote:

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

  This impacts all the documents that mention the FACIT-FATIGUE including, but not limited to:

  - eCRFs (RDC)
  - Tables, listings and figures (including mocks)
  - eCRF/ RDC guidelines
  - Reports (including ad-hoc requested reports)
  - Data Management Plan (DMP)

13.2.2.4 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: PGNAME.sas; Creation Date and Time: MMDDDYYYY HH:MM
Data Cutoff: DDMMMYY:HH:MM:SS – Listing Generated MMM DD, YYYY

and the following footer at the lower right corner:

Version Date Time Page x of y (for within output pagination)

where

PGNAME = SAS program name;
Version will be replaced by version number and "Draft" or "Final".

13.2.3 Statistical Specifications

13.2.3.1 Statistics Reported

- Unless otherwise specified, the mean and standard deviation (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

- Unless specified in the actual TLF shells for a study, all percentages will be rounded to one decimal place in all tables/listings/figures. Rounding will take place after all calculations have been performed.

- Use of N versus n:
  N = total number of subjects or subjects in the population.
  n = total number of subjects or subjects in the specific category.

- P-value label formatting

  Column heading **P-value**
  Row heading **P-value**
  Footnote – first word **P-value**
  Footnote – embedded word **p-value**

- All p-values should be reported to using SAS pvalue6.4 format (displayed as '0.xxxx' or '<0.0001')

13.2.4 SAS Procedure Output

All SAS log and output will be saved to file to a secure location for final archive.

13.2.5 Tables Summarizing Categorical Data

The following specifications apply to tables that summarize categorical data:

- Percent of events should be left blank (including the parentheses) if the number of events is zero.
- 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.

13.2.6 Subject Data Listings

In general, individual subject data listings should include all subjects with data. 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.

14.0 REFERENCE LIST

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ICH E3 (1996): 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): Guideline for Good Clinical Practice. 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).

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

SAS® for Windows® Version 9.3. SAS Inc. Cary, North Carolina USA.

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