Apellis

Protocol No: APL2-CP-AIHA-208

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)

PLAUDIT

Phase: II

Version: Amendment 4, Version 1.0

Date: 17 January 2019

SIGNATURE PAGE

Protocol APL2-CP-AIHA-208 was approved by:

PPD

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Date

Apellis Pharmaceuticals

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AMENDMENT 4: SUMMARY OF CHANGES FROM THE PREVIOUS VERSION

Updates to the protocol implemented in this amendment are provided in the table below. Where appropriate, deletions to the protocol have been marked by ~~strikethrough~~. Additions to the protocol have been marked by underline.

Protocol Versions		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment 4 Version 1.0	Amendment Date 17 January 2019	Global
Description of Change		Section(s) Affected by Change
Edits for clarity and to correct minor errors have been implemented that do not impact the study design and are therefore not described in detail in the table below.		Global
Through the protocol, screening to Day 336 has been designated as Part A, the "Core Study Phase". In addition, this protocol amendment enacts Part B, the "Long-Term Extension Phase", which will begin at Visit 15 (Day 336) and will continue indefinitely until the subject discontinues or the APL-2 development program is terminated.		Global
It was clarified that urinalysis tests will be performed at a local laboratory (through Footnote "N"). It was clarified that ferritin and vitamin B12/folate tests (Footnote "O")will be performed at a central laboratory, and Iron (Footnote "N")was moved to a separate line as iron will be tested at a local laboratory as originally indicated. Serum pregnancy test was removed at all timepoints following screening. This was an error correction; following screening urine pregnancy tests will be utilized as noted on the Part A Study Flow Chart. Footnote "Q" was added to clarify that: The use of silica reagents in coagulation panels should be avoided in subjects treated with APL-2. Footnote "R" was added to clarify that: At Visit 15 (Day 336; Week 48) subjects may elect to enter the Long-Term Extension Phase in order to continue to receive treatment with APL-2 indefinitely until the subject discontinues or the APL-2 development program is terminated. Subjects that elect to enter the Long-Term Extension Phase should complete study procedures as outlined in Section 17.3, Table 3. These subjects may initiate a different dose regimen of APL-2 and will be dispensed drug for home administration. Subjects that elect to enter the Long-Term Extension Phase and are confirmed to begin the intended Long-Term Extension Phase dose regimen of APL-2 (APL-2 1,080 mg twice weekly) should be instructed to skip their Core Phase Dose of APL-2 the day prior to Visit 15. Subjects that will enter the Long-Term Extension Phase but are expected to continue with their Core Phase Dose should take their regular dose APL-2 on the day prior to Visit 15. Footnote "S" was added to clarify that:		Part A Core Study Phase: Study Flow Chart (Table 1)

Some chemistry assessments may be performed at a central laboratory; see Section 13.1.7 for specification.	
It was clarified that: All data provided in the introduction is locked as of the approval date of the original protocol. Always see the most current version of the Investigator's Brochure for the most recent data for APL-2.	Section 4 Introduction
It has been noted that the use of silica reagents in coagulation panels should be avoided in subjects treated with APL-2. These reagents may interfere with PEGylated APL-2, resulting in artificially prolonged activated partial thromboplastin clotting time (aPTT). Additional information is provided in the Investigator's Brochure.	Section 7.3 Risk/Benefit Section 13.1.7.2 Hematology
It has been emphasized that subjects should be instructed to take their APL-2 treatment, as prescribed, and to contact the investigator immediately for guidance in the event of any missed doses. In subjects with PNH, discontinuation with APL 2 or noncompliance with the prescribed dose regimen has been observed to lead to the potential for an increased risk for serious hemolysis. The Sponsor's medical monitor should be contacted before interrupting or discontinuing treatment with APL-2.	Section 7.3 Risk/Benefit Section 11.3.3 Drug Administration
The following sentence was removed as endpoints will be assessed at the timepoints designated in the Study Flow Charts for both Part A and Part B. ~~Study endpoints will be assessed at months 2, 3, 6, and 12.~~	Section 8.2 Study Endpoints Synopsis
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 Part B Long-Term Extension Phase will continue indefinitely until the subject discontinues or the APL-2 development program is terminated. Subjects that elect to enter the Part B Long-Term Extension Phase should complete study procedures as outlined in Section 17.3 and Table 3. These subjects may initiate a different dose regimen of APL-2.	Section 9. Study Design Section 11.3.2 Planned Dose Levels and Dosing Schedule Section 12. Study Procedures Section 12.5 Long-Term Extension Phase
In order to align with guidance in the Investigator's Brochure, it was clarified that subjects must agree to use contraception and refrain from donating sperm for the duration of the study and ~~60~~ 90 days after their last dose of study drug.	Synopsis Section 10.1 Inclusion Criteria Section 10.1.1 Approved Methods of Contraception Section 13.6 Pregnancy Tests
The intended dose regimen for the Part B Long-Term Extension Phase is APL-2 1,080 mg twice weekly. It was noted that the body of the protocol contains information on APL-2 study treatments for the Part A Core Study Phase, and that the study treatment information for the Long-Term Extension Phase has been included in the Part B Long-Term Extension Phase Appendix 17.3.	Section 11. Study Treatments
It was noted that: Note: Study Procedures for Visit 15 (Day 336) may be different for subjects that elect to enter the Part B Long-Term Extension Phase. These subjects may initiate a different dose regimen of APL-2 and will be dispensed drug for home administration. If a subject is to enter the Part B Long-Term Extension Phase and it is confirmed that the subject will initiate the APL-2 dose regimen intended for use during the Long-Term Extension Phase (APL-2 1,080 mg twice weekly), the subject should be	Section 12.4.2 Outpatient Administration (Day 4 to Day 336)

instructed to skip their Core Study Phase dose the day before Visit 15. Subjects that will not initiate a new dose at Visit 15 should take their regular Part A Core Study Phase daily dose through Visit 15.	
It was clarified that the description of the scheduled end of study is applicable to subjects that complete the Part A Core Study Phase and continue to complete the study's follow-up visits (and do not continue into the Part B Long-Term Extension Phase). For these subjects, it was corrected that the study will last approximately ~~24~~ 15 months. Subjects that continue into the Part B Long-Term Extension Phase will continue treatment with APL-2 indefinitely until the subject discontinues or the APL-2 development program is terminated.	Section 12.6.3 Scheduled End of Study
It was clarified that a licensed physician or other licensed health care provider employed at the study site may perform the physical examination.	Section 13.1.2 Physical Examination
Plasma Hg was added to the hematology panel.	Section 13.1.7.1 Hematology
Indirect bilirubin, calcium, and phosphate were added to the serum chemistry panel.	Section 13.1.7.3 Serum Chemistry
It was clarified that for subjects that enter the Long-Term Extension Phase, the volumes noted in "Table 2: Blood Volume During Study (up to Day 420)" will continue to be collected as noted in the Study Flow Chart for the Part B Long-Term Extension Phase (Table 3).	Section 13.5 Blood Volume for Study Assessments
SAE outcomes were updated to align with the SAE form: Outcome may be classified as recovered/resolved, recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved, fatal, or unknown ~~resolved, improved, unchanged, worse, fatal or unknown (lost to follow-up)~~. References to "confinement" have been removed as subjects will not be confined in this study.	Section 14.2 Recording Adverse Event
The AE relationship categories and outcomes were updated to align with the current SAE form as follows: The PI will review each event and assess its relationship to study drug treatment (definitely related, possibly related, unlikely related, not related, unknown ~~unrelated, possibly, probably, likely~~). The date and time of onset, time relationship to drug dosing, duration, and outcome (~~resolved, improved, unchanged, worse, fatal, or unknown/lost to follow-up~~) of each event will be noted. The relatedness table in this section was also updated accordingly.	Section 14.4.1 Relationship of Events to Study Treatment
It was clarified that: All SAEs will be reported to the Safety Monitor by the PI via fax or email within 24 hours ~~one working day~~ of becoming aware of the event, whether or not the serious events are deemed drug-related.	Section 14.5 Serious Adverse Events
It was clarified that: WOCBP and males with female partners of child-bearing potential will be instructed to practice an acceptable method of birth control (as defined in Section 10.1.1) for the duration of the study and 90 days after their last dose of study drug.	Section 14.9 Pregnancy

If a female subject or partner of a male subject becomes pregnant during the study, the PI should report the pregnancy to the Safety Monitor within 24 hours of being notified using the pregnancy report form.	
Section 17.3 was added to contain information specific to the design and conduct of the Part B Long-Term Extension Phase. Any processes, procedure, or information not described in this Section is identical to that described through the body of the main protocol. 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 indefinitely until the subject discontinues or the development program is terminated. As described in Section 11, During the Part A Core Study Phase (up to Day 336) this study will utilize an acetate-buffered mannitol formulation of APL-2 (APL-2 270 mg/d and 360 mg/d). During the Part B Long-term Extension Phase subjects will transition to the planned Part B dose and formulation of APL-2, an acetate-buffered sorbitol formulation with APL-2 1,080 mg administered twice weekly by SC infusion (in addition, subjects may transition to APL-2 1,080 mg administered every three days [ie, a dose on every third day]; see Section 17.3.4.4for more details). Note: Some subjects may complete the Part A Core Study Phase prior to the availability of the acetate-buffered sorbitol formulation of APL-2 that is intended for use during the Long-Term Extension Phase. These subjects will continue with the same dose and formulation of APL-2 that they utilized during the Part A Core Study Phase until the sorbitol formulation is available. Table 4 provides the schedule of events for visits that will be conducted during the Long-Term Extension Phase.	Section 17.3 Part B: Long-Term Extension Phase

1. ABBREVIATIONS

ADL	Activities of daily living
AE	Adverse event
AIHA	Autoimmune Hemolytic Anemia
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BMI	Body mass index
BUN	Blood urea nitrogen
°C	Degrees Celsius
CABG	Coronary Artery Bypass Graft
CAD	Cold Agglutinin Disease
CIS	Carcinoma in situ
CK	Creatine kinase
Cmax	Peak serum concentration
cm	Centimeter
CrCl	Creatinine Clearance
CRF	Case report form
CS	Clinically significant abnormality
CTCAE	Common Terminology Criteria for Adverse Events
DAT	Direct Antiglobulin Test
dL	Deciliter
ECG	Electrocardiogram
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Unites States Foods and Drug Administration
FSH	Follicle-Stimulating Hormone
G	Gram(s)
GCP	Good clinical practice
GGT	Gamma-glutamyl transpeptidase
GLP	Good laboratory practice
Hb	Haemoglobin
HCV	Hepatitis C virus
hERG	Human ether-à-go-go-related gene
Hib	Haemophilus influenzae Type B (vaccine)
HSA	Human serum albumin
HV	Healthy Volunteer
IB	Investigator's brochure
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IEC	Institutional Ethics Committee
ITT	Intent-to-Treat
IV	Intravenous

Kg	Kilogram(s)
L	Litre(s)
LASA	Linear Analog Assessment Scale
LDH	Lactate dehydrogenase
LLN	Lower Limit of Normal
MAC	Membrane attack complex
MAVE	Major Adverse Vascular Event
MedDRA®	Medical Dictionary for Regulatory Activities
Mg	Milligram(s)
mL	Millilitre(s)
MOP	Manual of Procedures
µM	Micromolar; micromoles/L
NCS	Not clinically significant
NOEL	No observed effect level
NOAEL	No observed adverse effect level
PCV13	Pneumococcal conjugate vaccine
PD	Pharmacodynamic(s)
PEG	Polyethylene glycol
PEG40	Polyethylene glycol (40 kDa nominal molecular weight)
PI	Principal Investigator or designee
PK	Pharmacokinetic(s)
PPSV23	Pneumococcal polysaccharide vaccine 23
PT	Prothrombin time
PNH	Paroxysmal nocturnal hemoglobinuria
QTc	Corrected QT interval
QTcB	Bazett's correction
QTcF	Fridericia's correction
RBC	Red blood cell
SAA	Severe aplastic anaemia
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SMC	Safety Monitoring Committee
SOP	Standard operating procedure
$T_{½}$	Serum half-life
TEAE	Treatment-emergent adverse event
Tmax	Time at which Cmax is observed
ULN	Upper Limit of Normal
wAIHA	Warm Autoimmune Hemolytic Anemia
WBC	White blood cell
WHO	World Health Organization
WOCBP	Woman of Child-Bearing Potential

2. SYNOPSIS

Protocol Number	APL2-CP-AIHA-208
Official Tittle	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 Version and Date	Amendment 4; Version 1.0 17 January 2019
Compound	APL-2
Study Phase and Type	Phase II, open-label, evidence of safety, tolerability, efficacy, and pharmacokinetics pilot study.
Study Objectives	The objective of the study is to assess the safety, tolerability, preliminary efficacy, and pharmacokinetics of multiple subcutaneous (SC) doses of APL-2 in subjects with Warm Antibody Autoimmune Hemolytic Anemia (wAIHA) or Cold Agglutinin Disease (CAD)
Study Population	Subjects with a primary diagnosis of wAIHA or CAD.
Number of Subjects	The study is planned to enroll up to 24 subjects in two cohorts, up to 12 subjects with wAIHA in Cohort 1, and up to 12 subjects with CAD in Cohort 2.
Inclusion Criteria	1. At least 18 years of age. 2. Weight <125 Kg. 3. Subjects must have a primary diagnosis of wAIHA or CAD defined by the presence of hemolytic anemia and positive DAT for wAIHA (IgG) or CAD (C3). 4. Hemoglobin <11 g/dL. 5. Signs of hemolysis with abnormal values by any of the following hemolytic markers: a. Increased absolute reticulocyte counts (above ULN) b. Reduced haptoglobin (below LLN) c. Increased lactate dehydrogenase (LDH) (above ULN) d. Increased indirect bilirubin (above ULN) 6. Women of child-bearing potential (WOCBP) (defined as any female who has experienced menarche and who is NOT

permanently sterile or postmenopausal. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause) must have a negative pregnancy test at screening and must agree to use protocol defined methods of contraception for the duration of the study and 90 days after their last dose of study drug.

7. Males must agree to use protocol defined methods of contraception and agree to refrain from donating sperm for the duration of the study and 90 days after their last dose of study drug.
8. Able to provide documentary evidence of the following vaccinations within 2 years prior to screening:
    a. *Neisseria meningitides* types A, C, W, Y and type B (administered as two separate vaccinations)
    b. *Streptococcus pneumoniae* (Pneumococcal conjugate vaccine and Pneumococcal polysaccharide vaccine 23 [PCV13 and/or PPSV23, respectively])
    c. *Haemophilus influenzae* Type B (Hib) vaccine

    Subjects that do not have documentary evidence must be willing to receive any missing vaccinations as outlined below:
    a. *Neisseria meningitides* types A, C, W, Y and type B must be administered prior to dosing on Day 1. A booster is administered after at least 8 weeks (Day 56; for both vaccinations).
    b. *Streptococcus pneumoniae* PCV13 must be administered prior to dosing on Day 1 (see Section 12.2 for details). A PPSV23 booster is administered after at least 8 weeks (Day 56)
    c. *Haemophilus influenzae Type B* (Hib) must be administered prior to dosing on Day 1.
9. Willing and able to give informed consent.
10. **Specific for wAIHA**: Relapsed from, did not respond to, or did not tolerate at least one prior wAIHA treatment regimen (such as prednisone, rituximab).

Exclusion Criteria

1. Prior treatment with rituximab within 90 days.
2. Deficiency of iron, folic acid and vitamin B12 prior to treatment phase.
3. Abnormal liver function as indicated by elevated AST or ALT.

Any elevation of AST or ALT level >2x upper limit of normal (ULN) will require Sponsor review and approval for subject enrollment into the trial.

4. Elevated bilirubin not due to active hemolysis. Any elevation of bilirubin >ULN will require Sponsor review and approval for subject enrollment into the trial.
5. Active aggressive lymphoma requiring therapy or an active non-lymphatic malignant disease other than basal cell carcinoma or carcinoma *in situ* (CIS) of the cervix.
6. Presence or suspicion of active bacterial or viral infection, in the opinion of the Investigator, at screening or severe recurrent bacterial infections.
7. Participation in any other investigational drug trial or exposure to other investigational agent, device, or procedure within 30 days prior to screening period.
8. Pregnant, breast-feeding, or intending to conceive during the course of the study, including the Post-Treatment Phase.
9. Inability to cooperate or any condition that, in the opinion of the investigator, could increase the subject's risk by participating in the study or confound the outcome of the study.
10. Myocardial infarction, CABG, coronary or cerebral artery stenting and /or angioplasty, stroke, cardiac surgery, or hospitalization for congestive heart failure within 3 months or > Class 2 Angina Pectoris or NYHA Heart Failure Class >2
11. QTcF >470 ms
12. PR >280 ms
13. Mobitz II 2nd degree AV Block, 2:1 AV Block, High Grade AV Block, or Complete Heart Block unless the patient has an implanted pacemaker or implantable cardiac defibrillator (ICD) with backup pacing capabilities

Endpoints

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 subcutaneous (SC) APL-2.

Efficacy Endpoints:

- Change from baseline in Hb
- Number of red blood cell (RBC) transfusions during study

- Change from baseline in absolute reticulocyte count
- Change from baseline in LDH
- Change from baseline in haptoglobin
- Change from baseline in indirect bilirubin
- 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)
- APL-2 serum concentrations and pharmacokinetic (PK) parameters as appropriate

Exploratory PD markers include:

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

Planned Dose Level

Planned doses through the Part A Core Study Phase (screening to Day 336) will be as follows:

	Cohort 1 wAIHA N= up to 12	Cohort 2 CAD N= up to 12
Group 1	Daily SC doses of 270 mg for 12 months (n= up to 6)	Daily SC doses of 270 mg for 12 months (n= up to 6)
Group 2	Daily SC doses of 360 mg for 12 months (n= up to 6)	Daily SC doses of 360 mg for 12 months (n= up to 6)

Following Month 12 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. During the Part A Core Study Phase this study will utilize an acetate buffered mannitol formulation of APL-2 (for the 270 mg/d and 360 mg/d doses). During the long-term extension phase, subjects will transition to APL-2 doses of 1,080 mg twice weekly, and may transition to 1,080 mg every three days (ie, a dose on every third day) if necessary.

Note: Some subjects may complete the Part A Core Study Phase prior to the availability of the acetate buffered sorbitol formulation. These subjects will continue with their 270 mg/d or

	360 mg/d doses using the mannitol formulation until the acetate buffered sorbitol formulation is available.
Study Design	This is a Phase II, open-label, prospective, pilot study of APL-2 conducted in subjects with wAIHA or CAD in parallel. The Part A Core Study Phase will last for approximately 12 months (screening to Day 336). Following the Part A Core Study Phase, subjects may participate in Part B, the Long-Term Extension Phase in order to continue to receive treatment with APL-2 indefinitely until the subject discontinues or the development program is terminated. The study will consist of up to 24 subjects, up to 12 subjects with a primary diagnosis of wAIHA in Cohort 1, and up to 12 subjects with a primary diagnosis of CAD in Cohort 2. Subjects from each cohort will be randomly (1:1) assigned to receive either 270 mg/day or 360 mg/day of APL-2 treatment through Part A, for up to approximately 12 months (to Day 336). 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.
Statistical Methods	Treatment-emergent adverse events will be summarized by Cohort, dose group, System Organ Class and Preferred Term, in accordance with the Medical Dictionary for Regulatory Activities (MedDRA). Changes from baseline in efficacy outcomes will be summarized by Cohort and dose group using descriptive statistics. PK parameters will be computed from the individual serum concentrations-time data, using a non-compartmental approach and summarized by Cohort, dose group, and treatment time using descriptive analysis methods.

3. PART A CORE STUDY PHASE: STUDY FLOW CHART

The Study Flow Chart for Part B (Long-Term Extension Phase) is provided in Section 17.3.

Table 1: Part A Core Study Phase Study Flow Chart (Screening to Day 336)

Study Period	Screen	Baseline	Core Study Phase: Day 1 to Month 12													FU & Exit [L]	ETFU & ET [M]
Study Week	-4	1	1	1	1	2	4	8	12	16	20	24	32	40	48[R]	54 and 60	
Study Day	-30	1	2	3	7	14	28	56	84	112	140	168	224	280	336	378 and 420	
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16 and 17	
Visit Window (+/- Days)	0	0	0	0	2	2	7	7	7	7	7	7	7	7	7	7	NA
Informed Consent	X																
Demographics	X																
Medical and treatment history	X																
Inclusion/Exclusion criteria	X	X															
Vaccination [A]	X	X						X [A]									
Preventive antibiotic administration [B]		Daily ----------→[R]															
Physical examination [C]	X															X	X
Weight and Height	X																
Triplicate 12-lead electrocardiogram [D]	X	X					X	X	X	X	X	X	X	X	X	X	X
APL-2 administration [E]		Daily ----------→															
Injection site assessment [F]		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
Vital sign measurements [G]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis [O]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X
Blood [H]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics [I,O]		X			X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-APL-2 Ab assay [K,O]		X			X	X	X	X	X	X	X	X	X	X	X	X	X
LDH [N]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and chemistry [N, S]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X
Reticulocyte count [N]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X
Haptoglobin [O]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation profile [O, Q]	X	X					X		X		X		X	X	X		

Study Period	Screen	Baseline	Core Study Phase: Day 1 to Month 12													FU & Exit [L]	ETFU & ET[M]
Study Week	-4	1	1	1	1	2	4	8	12	16	20	24	32	40	48[R]	54 and 60	
Study Day	-30	1	2	3	7	14	28	56	84	112	140	168	224	280	336	378 and 420	
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16 and 17	
Visit Window (+/- Days)	0	0	0	0	2	2	7	7	7	7	7	7	7	7	7	7	NA
Complement profile (C3, CH50 & AH50)[O]	X	X				X	X	X	X	X	X	X	X	X	X	X	X
Flow cytometry for C3 deposition[O]	X	X				X	X	X	X	X	X	X	X	X	X	X	X
Plasma Hb[O]	X	X				X	X	X	X	X	X	X	X	X	X	X	X
Ferritin, vitamin B12/folate [O]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X
Iron[N]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy (B-HCG and FSH) [N]	X																X
DAT monospecific C3[O]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X
DAT monospecific IgG[O]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X
Immunoglobulins Quantitative (IgG, IgM and IgA) [O]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Cold Agglutinin Titer (at 4C) [for CAD subjects only][I][P]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test [J]		X				X	X	X	X	X	X	X	X	X	X	X	X
FACIT fatigue scale		X				X	X	X	X	X	X	X	X	X	X	X	X
LASA quality of life scale		X				X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug Dispensation for Home Administration				X	X	X	X	X	X	X	X	X	X	X	X	[R]	

FOOTNOTES:

A. If *Neisseria meningitides* vaccine/s are administered during screening (prior to dosing on Day 1), a booster (for both vaccinations) should be administered at least 8 weeks later (Day 56). If Pneumococcal vaccination is required during screening, a dose of PCV13 will be administered prior to dosing on Day 1 and a dose of PPSV23 will be administered at least 8 weeks later (Day 56). If the Hib vaccine is required, it must be administered prior to dosing on Day 1.

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 (Day 350). Note: Subjects unable to take the primary prophylactic antibiotic (penicillin) may instead take an alternative prophylactic antibiotic (erythromycin or azithromycin), which will be initiated at least 1 week prior to first dose of APL-2 and QTc interval confirmed prior to dosing with APL-2.

C. Full physical examination will be performed at the scheduled time points indicated. A symptom-driven physical examination may be performed at

various unscheduled time points if deemed necessary by the PI.

D. Triplicate 12-lead ECGs are to be performed before dosing and before blood sampling procedures.

E. Subjects will self-administer SC APL-2, after receiving appropriate training by a research nurse or other personnel. During site visits subject will self-administer APL-2 at the site. APL-2 will be dosed at the clinical site on Day 1 through Day 3.

F. Between site visits, subjects will be instructed to report any injection site reaction to the study coordinator.

G. On clinic dosing days vital signs will be measured within 2 hours before dosing, venipuncture, and ECG assessments. On clinic dosing days, vital signs will be measured within 30 minutes after dosing.

H. Blood samples will be taken pre-dose (exception see I below)

I. At Visit 2 only, PK samples will be taken pre-dose and at 4 hours post-dose.

J. Urine pregnancy test should be completed for women of child bearing potential (WOCBP) prior to dosing.

K. For subjects with positive anti-APL-2 antibody in last dose samples, additional samples of 6 and 12 months from last dose will be collected for further assessments.

L. Represents 2 six-week visits from weeks 54 to 60.

M. Subjects that discontinue should complete an early-termination follow-up visit 6 weeks (+/- 7 days) after treatment discontinuation, followed by an early termination visit 6 weeks (+/- 7 days) later.

N. These tests should be performed at a local laboratory.

O. These tests should be performed at a central laboratory.

P. These tests should be performed at both local and central laboratories.

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

R. At Visit 15 and the conclusion of Part A (Day 336; Week 48) subjects may elect to enter the Part B Long-Term Extension Phase in order to continue to receive treatment with APL-2 indefinitely until the subject discontinues or the APL-2 development program is terminated. Subjects who elect to enter the Part B Long-Term Extension Phase should complete study procedures as outlined in Section 17.3, Table 4. These subjects may initiate a different dose regimen of APL-2 and will be dispensed drug for home administration. Subjects that elect to enter the Part B Long-Term Extension Phase and are confirmed to begin the intended Part B dose regimen of APL-2 (APL-2 1,080 mg twice weekly) should be instructed to skip their Part A dose of APL-2 the day prior to Visit 15. Subjects who will enter the Part B Long-Term Extension Phase, but are expected to continue with their Part A dose, should take their regular dose APL-2 on the day prior to Visit 15.

S. Some chemistry assessments may be performed at a central laboratory; see Section 13.1.7 for specification.

4. INTRODUCTION

All data provided in the introduction is locked as of the approval date of the original protocol. Always see the most current version of the Investigator's Brochure for the most recent data for APL-2.

4.1 Background

This study is being conducted as part of a series of studies for the clinical development of APL-2. The trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements. The subject population will be comprised of adult male and female subjects with wAIHA or CAD.

4.1.1 APL-2

APL-2 is a small 13-amino acid cyclic peptide with 12 natural amino acids and a single unnatural amino acid (methyltryptophan) covalently coupled via a linker to each end of a linear 40 kDa PEG chain, thus, there are two peptide moieties per molecule of APL-2. The peptide portion of the drug binds to primate complement C3 and exerts a broad inhibition of the complement cascade, a biological process that is part of innate immunity and is involved in multiple inflammatory processes. The PEGylation imparts longer residence time in the body after administration of the drug.

APL-2 is being developed for the management of paroxysmal nocturnal hemoglobinuria (PNH), an indication for which the subcutaneous (SC) route of administration is being employed.

Recent studies have suggested that massive opsonization of PNH erythrocytes by C3 fragments is observed in patients receiving eculizumab treatment (Risitano, 2009; Hill, 2007). This opsonization is believed to cause the removal of erythrocytes by the spleen and the liver, resulting in extravascular hemolysis. The extravascular hemolysis can be very significant in a subset of eculizumab-treated PNH patients and is believed to be a major contributor to the lack of complete eculizumab response in most patients. It is reasonable, therefore, to expect that a treatment able to inhibit both MAC formation and C3 opsonisation will provide improved therapeutic benefit to PNH patients, compared to eculizumab.

In fact, phase 1 clinical experience has demonstrated that APL-2 provides sustained inhibition of hemolytic activity in PNH patients who have never received eculizumab (Protocol APL2-CP-PNH-204, New Zealand) and in patients receiving eculizumab (Protocol APL-CP0514, US) who continue to require transfusions due to ongoing hemolysis.

4.1.2 Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemia (AIHA) is a rare autoimmune disease characterized by hemolysis mediated by autoantibodies directed against self-red blood cells (RBC), with the incidence of 1-3 per 100,000/year and overall mortality rate of approximately 11% (Park, 2016). AIHA is classified as either warm antibody (60-70%), or cold agglutinin disease (CAD, 20-25%), depending upon the temperature at which the autoantibodies show maximum binding

(Barcellini, 2015). Warm antibody AIHA (wAIHA) is mediated by warm reactive autoantibodies, which are usually of the immunoglobulin G class (IgG). Almost 90% of CAD is medicated by monoclonal antibodies of IgM class (Reynaud, 2015). The diagnosis of wAIHA or CAD is based on the presence of hemolytic anemia, signs of hemolysis with reticulocytosis, low haptoglobin, increased lactate dehydrogenase, elevated indirect bilirubin, and a positive direct antiglobulin test (DAT) for IgG or and/or complement C3 (Bass, 2014). The degree of anemia at presentation correlates with the severity of AIHA and with the probability of relapse (Wouters, 2015).

4.1.3 Rational for Treatment with APL-2

Complement plays an important role in warm antibody AIHA. On erythrocytes heavily coated with immunoglobulin, the amount of antigen-antibody complex can be sufficient for binding complement protein complex C1 and, thereby, for activation of the classical complement pathway. Moreover, complement activation plays a significant role in CAD, which is entirely a complement-dependent disorder (Berentsen, 2015). Cold antibodies (IgM) temporarily bind to the RBC membrane, activate complement, and deposit complement factor C3 on the cell surface. These C3-coated RBCs are cleared slowly by the macrophages of the liver through extravascular hemolysis. Less frequently, the complete complement cascade is activated on the cell surface, resulting in the insertion of membrane attack complex C5b to C9 and intravascular hemolysis (Dhaliwal, 2004).

Current available treatments for patients with AIHA are far from satisfactory. Available treatments include steroids, RBC transfusions, immunosuppressants, splenectomy, and Rituximab off label use. Long-term use of corticosteroids is known to be associated with many complications. RBC transfusions may exacerbate hemolysis with the potential risk to develop hyperhemolysis and RBC alloantibodies resulting in an inadequate recovery due to autoantibodies will react with donor cells in AIHA patients (Wouters, 2015). RBC transfusions should be restrictive and specific precautions need to be undertaken to avoid severe transfusion reactions and alloimmunization with increased transfusion problems (Berentsen, 2015). On the other hand, the sustained response rate for wAIHA after splenectomy is approximately 60-70% according to the most recent data with a peri-operative risk and a mortality rate of less than 1% (Reynaud, 2015). However, overwhelming sepsis and post-operative cytotoxic immunosuppressants can also be associated with serious adverse events. Treatment with Rituximab monotherapy has been shown in prospective studies to induce remission in approximately half of the patients with CAD, although complete remissions are unusual and the medical response duration is only 1 year (Berentsen, 2015). Given the toxicity of rituximab and concern of adverse effects, a balanced assessment of benefit and risk should be considered in treating AIHA patients (Berentsen, 2012).

In addition, all these therapeutic approaches need time to become effective. In patients presenting with acute symptomatic AIHA or experiencing an exacerbation of AIHA, the primary goal of treatment is to halt the acute hemolysis. Moreover, restoration of oxygen carrier in symptomatic anemia is mandatory. Therefore, treatment with complement inhibitors of complement cascade may halt or at least attenuate acute complement mediated hemolysis in these patients and improve recovery of RBC destruction in AIHA patients.

In recent years, an increased interest in the role of complement inhibition in AIHA has been observed and preliminary findings in numerous studies are encouraging. TNT003, an inhibitor of C1s, prevented the classical pathway driven complement C3 deposition on RBCs and hemolysis as seen in an ex vivo hemolysis assay using plasma samples isolated from CAD patients (Shi, 2014). TNT009, an antibody directed against C1s, showed a rapid abrogation of extravascular hemolysis, normalized bilirubin levels, and decreased the destruction of reticulocytes in 3 of 4 CAD patients within 24 hours. Haptoglobin levels normalized within one week of treatment and completely normalized hemoglobin levels (Hb > 12 g/dL) were observed after the 4-week dosing period in two patients (LB2237, EHA21, 2016).

Based on scientific and clinical evidence of the role of complement in AIHA, APL-2 has the potential to prevent C3-mediated extravascular and MAC mediated intravascular hemolysis in AIHA patients. An overview of available information regarding APL-2 follows below. Further details can be found in the APL-2 Investigator's Brochure.

5. NON-CLINICAL DATA

Further details can be found in the APL-2 Investigator's Brochure.

5.1 Pharmacology

Primary pharmacology studies were performed with APL-2. *Ex vivo* studies conducted with blood from PNH patients revealed that APL-2 can protect PNH RBC from complement-mediated lysis and also prevent RBC opsonization by C3 fragments (i.e. C3 loading). The studies combined a modified Ham's test with flow cytometry. Blood from PNH patients was acidified in the presence of magnesium in order to activate the alternative complement pathway and lyse the PNH erythrocytes. The cells were incubated in the presence of magnesium only (negative control), eculizumab (Soliris®, an anti-C5 antibody approved to treat PNH and used as a positive control/comparator) or APL-2. The surviving erythrocytes, including normal and PNH RBCs, were then labeled with anti-CD59 and anti-C3d and analyzed using standard flow cytometry to assess protection against hemolysis. APL-2 was as effective as eculizumab in protecting PNH RBCs against direct MAC-mediated hemolysis, and, unlike eculizumab, it was also effective in preventing massive opsonization of those cells by C3 fragments. Based upon the available *ex vivo* and clinical data, the efficacious dose for humans has been estimated to be between 2 mg/kg/d and 4 mg/kg/d.

During safety pharmacology studies, APL-2 produced little or no reduction in human ether-à-go-go-related gene (hERGz) current amplitude when tested *in vitro* over a concentration range of 1 µM to 300 µM in the presence or absence of human serum albumin (HSA). Similarly, APL-2 had no effects on body temperature or on respiratory and cardiovascular parameters when administered to telemeterized cynomolgus monkeys administered up to a single 140 mg/kg dose.

5.2 Pharmacokinetics

PK parameters have been assessed after IV (single dose, slow bolus injection) and SC (single dose and 7-day multiple-dose) administrations of APL-2 to cynomolgus monkeys. After a single IV dose, peak serum concentrations (C_{max}) were achieved on Day 3, followed by exponential declines from Day 4 to 15. APL-2 was readily absorbed from SC depots (estimated bioavailability ~85%), and serum SC concentrations after 3 days were similar to those achieved 3 days after IV administration of the same dose. Repeated daily SC administrations of APL-2 caused continuously increasing serum concentrations until cessation of dosing or the reaching of a steady state. After cessation of dosing, APL-2 levels decreased in an exponential manner with an apparent serum half-life ($t_{½}$)of ~7.5 days.

The PK behavior of APL-2 is typical of a PEGylated peptide and is characterized by a systemic $t_{½}$ comparable to many antibodies. Notably, the serum C_{max} for APL-2 at all doses tested in the monkey and rabbit toxicology studies exceeded the exposures needed to demonstrate activity in the *ex vivo* PNH model based on the modified Ham's assay (≥100 µg/mL).

5.3 Toxicology

The safety of APL-2 has been evaluated in pivotal repeat-dose toxicity and genetic toxicology studies conducted in accordance with FDA GLP regulations. Overall, APL-2 has displayed a favorable tolerability profile when administered subcutaneously to both New Zealand White rabbits and cynomolgus monkeys, with only weak to mild immunogenicity observed in rabbits and little to no immunogenicity observed in monkeys. Microscopic changes consistently observed with repeat-dose administration up to 6 months in rabbits and 9 months in monkeys included single- or multi-organ macrophage vacuolation and tubular degeneration of the kidney. Macrophage vacuolation is an adaptive change associated with the clearance of large molecules (e.g. PEG40) from the tissues and, as expected, was lacking of any behavioral or clinical correlates. Renal tubular degeneration was observed with increased incidence and/or at lower doses in rabbits between 28 days and 6 months, and increased incidence in monkeys between 28 days and 9 months. The severity of the kidney findings (i.e., minimal to mild) did not increase over time in either species. Furthermore, target organ toxicity in the kidneys has also been associated with administration of PEG in animals (Rudmann, 2013). Most of the toxicological observations noted in the APL-2 groups were comparable to those noted in the groups of animals receiving PEG40. Although noted in animal species, the macrophage vacuolation or kidney toxicity has not been associated with either behavioral or clinical effects in animals nor with any serious adverse events in humans (Ivens, 2013).

APL-2 was not shown to be mutagenic in two *in vitro* Ames assays, nor aneugenic or clastogenic in both an *in vitro* micronucleus assay in TK6 cells and an *in vivo* micronucleus assessment in CD-1 mice.

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

6. CLINICAL DATA

To date, two Phase I trials in healthy volunteers (HV) have been conducted in order to assess safety and PK parameters of APL-2 administered as a SC injection and to guide dose selection for trials in PNH subjects. A single Phase I single ascending dose has evaluated intravenous (IV) dosing of APL-2 in HV. Two ongoing trials are evaluating APL-2 delivered by SC injection in PNH patients (see Table 2 for details).

Table 2. Summary of all clinical studies of APL-2 (up to March 2017).

Protocol Number /Phase/Status	Protocol Title	Study Population Subjects Planned/Treated	Endpoints	Planned Dosage Regimen
SUBCUTANEOUS				
APL-CP0713-1 Phase I (Complete)	A Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of SC APL-2 in Healthy Adult Subjects	31 healthy volunteers APL-2: 24/24 Placebo: 7/7	Safety, tolerability, PK and PD of single ascending doses (SAD) of APL-2	SAD: 45, 90, 180, 360, 720, 1440 mg Single dose
APL-CP1014 Phase I (Complete)	Phase 1, Double-blind, Randomized, Multiple Ascending APL-2 Dose Study in Healthy Volunteers	20 healthy volunteers APL-2: 16/6 Placebo: 4/4	Safety, tolerability, PK and PD of multiple ascending (MAD) doses of APL-2	MAD: 30, 90, 180, 270 mg/day for 28 days
APL-CP0514 Phase I (Ongoing)	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 PNH.	12 patients with PNH – Eculizumab APL-2: 12/12[1]	Safety, tolerability, PK and PD	Cohort 1: 25 mg single dose followed by 28 days washout then 5 mg/day for 28 days Cohort 2: 50 mg single dose followed by 28 days washout then 30 mg/day for 28 days Cohort 3: 180 mg/day for 28 days Cohort 4: 270 mg/day for up to 365 days (ongoing)
APL2-CP-PNH-204 Phase Ib (Ongoing)	A Phase Ib, Open Label, Multiple Ascending Dose, Pilot Study to Assess the Safety, Preliminary Efficacy and Pharmacokinetics of Subcutaneously Administered APL-2 in Subjects with PNH. – PADDOCK –	12 patients with PNH - Eculizumab naïve APL-2: 6/6[2]	Safety, tolerability, PK and PD	Cohort 1: 180 mg/day for 28 days[3] Cohort 2: 270 mg/day for up to 365 days (ongoing)
INTRAVENOUS				
APL2-CP-HV-401 Phase I (Clinical phase complete)	A Phase 1, Double-blind, Randomized, Placebo-Controlled, Single Ascending Dose Study of Intravenous APL-2 in Healthy Volunteers	20 healthy volunteers APL-2: 16/16 Placebo: 4/4	Safety, tolerability, PK and PD of SAD APL-2	SAD: 200, 600, 1500 and 2300 mg IV - Single dose

[1] One subject is included in 3 cohorts and is counted three times and one subject is included in two cohorts and is counted twice.

[2] One subject is included in 2 cohorts and is counted twice.

[2] One subject received only a single dose of 180 mg then withdrew consent.

6.1 Completed Clinical Trials in Healthy Volunteers

CCI

Further details can be found in the APL-2 Investigator's Brochure.

6.2 Ongoing Clinical Trials

There are two ongoing clinical studies testing APL-2 administered SC in PNH patients (APL-CP0514 and APL-2-CP-PNH-204). An interim analysis has been performed for both studies with a data cut at 85 days of treatment for all subjects and draft data is available.

- APL-CP0514 is a Phase Ib, open-label study being conducted at multiple clinical sites in the United States to assess the safety, tolerability, PK and PD of APL-2 as an add-on to standard of care in subjects with PNH. The study is comprised of 4 cohorts in total; 3 cohorts (Cohorts 1-3) with two subjects per cohort, and one cohort with six subjects (Cohort 4). Cohorts 1 to 3 have completed and Cohort 4 is ongoing. All six subjects in Cohort 4 have completed at least 3 months of treatment with APL-2 270 mg/d. Based on the clinical benefit observed all subjects entered an extension phase allowing them to continue to receive dosing with APL-2 for up to 1 year.
- APL-2-CP-PNH-204 is a Phase Ib, open-label study in patients with PNH who are not receiving eculizumab. The study is comprised of two cohorts of 3 subjects each at dose of 180 and 270 mg/d were planned for evaluation. Cohort 1 has completed and Cohort 2 is ongoing. All three subjects entered into Cohort 4 have completed 3 months of treatment with APL-2 270 mg/d. Based on the clinical benefit observed all 3 subjects were eligible to enter an extension phase allowing them to continue to receive dosing with APL-2 for up to 1-year. One subject withdrew for personal reasons; 1 subject entered the extension phase and received daily doses of APL-2 for >8 months including doses of 360 mg for >3 months, but was diagnosed with a malignancy, unrelated to the study drug, and treatment was withdrawn in April 2017; and the remaining subject continues to receive APL-2 270 mg/d.

Across the two studies, a total of 13 subjects with PNH have been dosed with APL-2, with 8 having received ≥270 mg/d for >3 months including 2 who have received 360 mg/d for 2 months. APL-2 has been generally well tolerated in these subjects. At approximately 2-month intervals, all safety data from each study is reviewed by members of an independent safety monitoring committee (SMC) who are responsible for providing recommendations with respect to monitoring and continuation of the studies.

As of the safety cut-off date for the 2017 IB, there have been a total of eleven SAEs reported in five out of nine subjects across the two trials. Of these, six are considered to be unrelated to APL-2 and three have been assigned a causality of 'possibly related' to APL-2 by the Sponsor. Those that are considered possibly related include hypersensitivity reaction, and increased ALT x 2 reports in the same subject.

7. RATIONALE

7.1 Purpose of the Study

This study will be the initial exploration of APL-2 in patients 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. The assessments of safety, tolerability, preliminary efficacy, PK, and PD following administration of multiples doses of APL-2 will guide decisions to further develop the drug.

7.2 Dose Selection

7.2.1 Part A: Core Study Phase

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

The toxicological data accumulated from the animal studies were used to guide dose selection during the Phase I single ascending dose and multiple ascending dose studies in HVs (protocols APL-CP0713-1 and APL-CP1014 respectively). In particular, the highest doses were selected based on exposure predicted by the PK model and compared with the exposures measured at the no observed adverse effect level (NOAEL) in monkeys.

The starting dose for this trial will not exceed the highest dose tested in the multiple ascending dose study in HVs, and Phase I studies of PADDOCK and PHAROAH studies in patients with PNH, which was found to be well-tolerated. At the time of initiation of this study, the dose selected for any cohort or individual subject will not exceed 360 mg/day (estimated to reach approximately 85 % of the C_{max} of the NOAEL observed in monkeys) without a protocol amendment. Doses of 270 mg/d and 360 mg/d that are used for on-going Phase I studies in patients with PNH and will be examined in patients with AIHA.

The rationale for including the 360 mg/day dose is:

- A dose of 270 mg/day of APL-2 as adjunct therapy to eculizumab was shown to be effective in the US phase 1b study APL-CP0514 in PNH patients exhibiting a suboptimal response to eculizumab. Notably, 5 of the 6 subjects in this study were receiving eculizumab at doses or frequencies above the labeled regimen. Since the target of APL-2, C3, is upstream of the eculizumab target C5, APL-2 is expected to have at least two key effects: reduction of C3b opsonization that leads to extravascular hemolysis and

reduction of downstream C5 that mediates intravascular hemolysis. Encouraging signs of activity were also observed with APL-2 monotherapy in 3 treatment-naïve PNH patients in the New Zealand phase 1b study APL-2-CP-PNH-204; however, variability in observed responses in this small population suggests additional dose-ranging higher than 270 mg, may be warranted.

- The proposed APL2-CP-AIHA-208 monotherapy trial in AIHA patients targets only C3. Given the incomplete understanding of APL-2 monotherapy dose-response in PNH patients as described above, the inclusion of two doses of APL-2, 270 mg/day and 360 mg/day, in the proposed AIHA study will support identification an optimal dose for this new disease indication as a C3 complement inhibition monotherapy.

- The proposed 360 mg/day dose is estimated to reach approximately 73% of the Cmax of the NOAEL observed in monkeys after 273 days SC dosing. In addition, Apellis has completed two clinical studies investigating the safety, tolerability, and PK of single APL-CP-0713-1 subcutaneous doses (including 360 mg, and a maximum dose of 1440 mg), and single APL2-CP-HV-401 intravenous doses (up to 2300 mg) of APL-2 in healthy volunteers. Maximum doses from both of these studies appeared to be safe and well tolerated and are estimated to reach approximately 23% and 65% respectively of the Cmax of the NOAEL observed in monkeys. Further support of safety and tolerability comes from emerging data from 2 patients receiving APL-2 360 mg/day for up to 2 months in the ongoing PNH Phase 1b trials.

The self-administration pump can be programmed to deliver in volumes of one mL increments, and no fractions of thereof. As a result, when delivering a dose of 270 mg, a nominal dose of up to 280 mg may be delivered dependent upon the concentration of the formulation (e.g. formulation 40 mg/mL administered in 7mL provides a dose of 280 mg). This difference of approximately 4% is considered an acceptable margin which will have minimal/no impact on the PK/PD or efficacy of APL-2.

7.2.2 Part B: Long-Term Extension Phase

Following Day 336 and the completion of Part A, the 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. During Part A this study will utilize an acetate buffered mannitol formulation of APL-2 (for the 270 mg/d and 360 mg/d doses). During Part B subjects will transition to doses of 1,080 mg twice weekly, and may transition to 1,080 mg every three days (ie, a dose on every third day) if necessary. The dose rationale for the Part B Long-Term Extension Phase is provided in Section 17.3.3.

7.3 Risk/Benefit

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

The volume of blood planned for collection from each subject over the course of the study (see Section 13.4) will be minimized in order to limit the impact on the overall health of these anemic subjects.

Systemic complement inhibition might predispose individuals to infections caused by encapsulated organisms, including *Streptococcus pneumoniae*, *Neisseria meningitides*, and *Haemophilus influenza Type B*. In addition to the vaccinations against these encapsulated organisms, prophylactic antibiotic therapy (penicillin V 500 mg twice a day) will be prescribed to all subjects at the initiation of dosing (Day 1) and continue for two weeks after the final dose of APL-2 (e.g. until Day 350) to minimize potential infection risk. Body temperature and vital signs will be monitored periodically, and relevant blood parameters monitored regularly throughout the study to assess for signs of infection. The Principal Investigator (PI) should be contacted immediately in the event of a suspected infection despite prophylactic antibiotic treatments for guidance and appropriate action to be taken.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on beta-lactam antibiotic (e.g. penicillin, amoxicillin, etc.) therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity. Before initiating therapy with penicillin V, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins or cephalosporins. Subjects with a known hypersensitivity to penicillin/amoxicillin may be prescribed erythromycin 500 mg twice daily, or Azithromycin 500 mg 3 times per week as alternative treatment at the outset (see Section 11.4 for details).

Other frequently reported adverse effects in patients taking penicillin are diarrhea/loose stools, nausea, skin rashes, urticaria and vomiting. Patients should, therefore, be advised that these reactions may occur. Treatment may be switched to erythromycin 500 mg twice daily (see Section 11.4 for details) if there is evidence of penicillin-related intolerability (such as nausea and diarrhea).

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

Details regarding the dosing regimen and administration of APL-2 are provided in Section 11 (Part A) and Section 17.3.4 (Part B). Subjects should be instructed to take their APL-2 treatment as prescribed, and to contact the investigator immediately for guidance in the event of any missed doses. In subjects with PNH, discontinuation with APL-2 or noncompliance with the

prescribed dose regimen has been observed to lead to the potential for an increased risk for serious hemolysis. The Sponsor's medical monitor should be contacted before interrupting or discontinuing treatment with APL-2.

There is a potential health benefit for trial participants from receipt of study drug. At the proposed dose levels of APL-2, a significant decrease in complement-mediated hemolytic activity was observed in all APL-2-treated subjects (both treatment-naïve and treated previously with eculizumab) in PNH Phase 1 studies and in HV studies. APL-2 may, therefore, reduce complement-mediated hemolytic activity in AIHA patients. In this context, a careful evaluation of the risk/benefit ratio should be made. APL-2 at the proposed doses has been deemed safe for up to 9 months of administration in preclinical studies and 28 days in HV studies. In addition, in studies of subjects with PNH (See Section 6.2), ongoing treatment with APL-2 270 mg/d or 360 mg/d has been well-tolerated for at least 2 months, and has provided clinical benefit to subjects either treated alone or as an add-on to eculizumab.

If efficacious and safe, APL-2 is expected to continue to improve Hb levels and reduce transfusion dependency in these patients throughout the Part A treatment period of 336 days (the Core Stud Phase) and beyond (through the Part B Long-Term Extension Phase).

8. STUDY OBJECTIVES AND ENDPOINTS

8.1 Study Objectives

The objectives of the study are to assess safety, tolerability, preliminary efficacy and PK of multiple SC doses of APL-2 in subjects with 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 PD of multiple SC doses of APL-2 when administered to AIHA patients.

8.2 Study Endpoints

Primary Safety Endpoints:

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.

Efficacy Endpoints:

- Change from baseline in Hb
- Number of red blood cell (RBC) transfusions during study
- Change from baseline in absolute reticulocyte count
- Change from baseline in LDH
- Change from baseline in haptoglobin
- Change from baseline in indirect bilirubin
- APL-2 serum concentrations (and pharmacokinetic (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)

Exploratory PD markers include:

- Complement (e.g., CH50, AP50, and C3) activity and levels
- C3 deposition on RBC cells

9. 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, up to 12 subjects with a primary diagnosis of wAIHA in Cohort 1 and up to 12 subjects with a primary diagnosis of CAD in Cohort 2. Subjects in each cohort will be randomly (1:1) assigned to receive either 270 mg/d or 360 mg/d of APL-2 treatment 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 in Section 17.3.1.

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 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.

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), PCV13 or PPSV23, and 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 PI. During study, the first 3 daily SC doses of APL-2 (Day 1 to 3) as well as doses on Day 7 and 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.

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 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).

10. SUBJECT SELECTION

The study is planned to enroll up to 24 subjects, with up to 12 subjects in Cohort 1 with a primary diagnosis of wAIHA and up to 12 subjects in Cohort 2 with a primary diagnosis of CAD.

Subjects should not be rescreened once they have been designated as a screen failure, unless this is discussed in advance and documented in writing with the sponsor.

10.1 Inclusion Criteria

At Screening (unless otherwise specified), subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. At least 18 years of age.
2. Weight <125 Kg.
3. Subjects must have a primary diagnosis of wAIHA or CAD defined by the presence of hemolytic anemia and positive DAT for wAIHA (IgG) or CAD (C3).
4. Hemoglobin <11 g/dL.
5. Signs of hemolysis with abnormal values by any of the hemolytic markers:
    a. Increased absolute reticulocyte count (above ULN)
    b. Reduced haptoglobin (below LLN)
    c. Increased lactase dehydrogenase (LDH) (above ULN)
    d. Increased indirect bilirubin (above ULN)
6. Women of child-bearing potential (WOCBP) (defined as any female who has experienced menarche and who is NOT permanently sterile or postmenopausal. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause) must have a negative pregnancy test at screening and must agree to use protocol defined methods of contraception for the duration of the study and 90 days after their last dose of study drug.
7. Males must agree to use protocol defined methods of contraception and agree to refrain from donating sperm for the duration of the study and 90 days after their last dose of study drug.
8. Able to provide documentary evidence of the following vaccinations within 2 years prior to screening:
    a. *Neisseria meningitides* types A, C, W, Y and type B (administered as two separate vaccinations)
    b. *Streptococcus pneumoniae* (Pneumococcal conjugate vaccine and Pneumococcal polysaccharide vaccine 23 [PCV13 and/or PPSV23, respectively])
    c. *Haemophilus influenzae* Type B (Hib) vaccine

Subjects that do not have documentary evidence must be willing to receive any missing vaccinations as outlined below:

a. *Neisseria meningitides* types A, C, W, Y and type B must be administered prior to dosing on Day 1. A booster is administered after at least 8 weeks (Day 56; for both vaccinations).

b. *Streptococcus pneumoniae* PCV13 must be administered prior to dosing on Day 1 (see Section 12.2 for details). A PPSV23 booster is administered after at least 8 weeks (Day 56)

c. *Haemophilus influenze Type B* (Hib) must be administered prior to dosing on Day 1.

9. Willing and able to give informed consent.
10. **Specific for wAIHA**: Relapsed from, did not respond or relapsed, or did not tolerate, at least one prior wAIHA treatment regimen (such as prednisone, rituximab).

10.1.1 Approved Methods of Contraception

Approved methods of contraception include: oral contraceptives, intrauterine device, medically acceptable barrier methods (diaphragm or condom), implantable or injectable contraceptives (like Depo-Provera) or removable birth control device (like NuvaRing® or Ortho Evra patches); and/or surgical sterilization (at least 6 months before dosing). Subjects practicing abstinence and coitus interruptus (pull out method) must agree to use an additional approved method of contraception during the study and 90 days after their last dose of study drug.

10.2 Exclusion Criteria

Subjects will be excluded from the study if there is evidence of any of the following criteria at screening or check-in, as appropriate.

1. Prior treatment with rituximab within 90 days.
2. Deficiency of iron, folic acid and vitamin B12 prior to treatment phase.
3. Abnormal liver function as indicated by elevated AST or ALT. Any elevation of AST or ALT level >2x upper limit of normal (ULN) will require Sponsor review and approval for subject enrollment into the trial.
4. Elevated bilirubin not due to active hemolysis. Any elevation of bilirubin >ULN will require Sponsor review and approval for subject enrollment into the trial.
5. Active aggressive lymphoma requiring therapy or an active non-lymphatic malignant disease other than basal cell carcinoma or CIS of the cervix.
6. Presence or suspicion of active bacterial or viral infection, in the opinion of the Investigator, at screening or severe recurrent bacterial infections.
7. Participation in any other investigational drug trial or exposure to other investigational agent, device, or procedure within 30 days prior to screening period.

8. Pregnant, breast-feeding, or intending to conceive during the course of the study, including the Post-Treatment Phase.
9. Inability to cooperate or any condition that, in the opinion of the investigator, could increase the subject's risk by participating in the study or confound the outcome of the study.
10. Myocardial infarction, CABG, coronary or cerebral artery stenting and /or angioplasty, stroke, cardiac surgery, or hospitalization for congestive heart failure within 3 months or > Class 2 Angina Pectoris or NYHA Heart Failure Class >2
11. QTcF > 470 ms
12. PR > 280 ms
13. Mobitz II 2nd degree AV Block, 2:1 AV Block, High Grade AV Block, or Complete Heart Block unless the patient has an implanted pacemaker or implantable cardiac defibrillator (ICD) with backup pacing capabilities

11. STUDY TREATMENTS

This section contains study treatment information for Part A (screening through Day 336; the Core Study Phase). Study treatment information for the Part B Long-Term Extension Phase is provided in Section 17.3.4.

11.1 Allocation to Treatment

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be scheduled to enter the study. Up to 12 subjects for each type of AIHA (wAIHA or CAD) will be randomly (1:1) assigned to receive either 270 mg/d or 360 mg/d of APL-2 treatment for up to 12 months for Part A, the Core Study Phase.

11.2 Blinding

None; this is an open-label study.

11.3 Treatments Administered

Sterile solutions of APL-2 up to 40 mg/mL in acetate-buffered mannitol, administered SC.

11.3.1 Drug supplies

11.3.1.1 Identity of Investigational Products

APL-2 will be supplied as a sterile solution of APL-2 in acetate-buffered mannitol, at concentrations of up to 40 mg/mL, supplied in stoppered glass vials.

11.3.1.2 Study Supplies

The Sponsor will supply sufficient quantities of APL-2 drug product to allow completion of this study. The lot numbers, manufacture dates, and expiration dates of the drugs supplied will be recorded in the final report. The Sponsor will also supply syringes, vial adapters, infusion sets and ambulatory syringe infusion pumps (e.g. Crono Super- PID, FreedomEdge, etc.) as required. APL-2 in acetate-buffered solutions should be stored refrigerated at 2-8°C.

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

11.3.1.3 Accountability

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

At the conclusion of the study, any unused investigational product will either be destroyed at the clinical site or be returned to the Sponsor or designee for destruction, and destruction will

be documented appropriately. If no supplies remain, this fact will be documented appropriately.

11.3.2 Planned Dose Levels and Dosing Schedule

Starting on Day 1 (Visit 2), subjects will receive SC APL-2 daily for up to 336 days at the corresponding dose.

Planned doses will be as follows:

	Cohort 1: wAIHA (n=12)	Cohort 2: CAD (n=12)
Group 1	Daily SC doses of 270 mg for 12 months (n=6)	Daily SC doses of 270 mg for 12 months (n=6)
Group 2	Daily SC doses of 360 mg for 12 months (n=6)	Daily SC doses of 360 mg for 12 months (n=6)

Subjects in each cohort will be randomly (1:1) assigned to receive either APL-2 270 mg/d or APL-2 360 mg/d at Day 1, and will continue treatment through Day 336 (Part A, the Core Study Phase).

The first SMC meeting will be scheduled once 4 enrolled subjects complete 28 days of dosing (or at an earlier time point in order to review subject data), and subsequent SMC meetings will be held at 6-month intervals throughout the study.

A. At Visit 15 (Day 336) and the conclusion of Part A, subjects are eligible to continue to receive treatment with APL-2 through Part B, the Long-Term Extension Phase. These subjects should not complete follow-up procedures but will continue participation in the study indefinitely until the subject discontinues or the development program is terminated. Section 17.3 provides information on the conduct of the Long-Term Extension Phase.

11.3.3 Drug Administration

Dose volumes can range between 7-10 mL, these doses will be administered as SC infusions.

The preferred site of injection will be the abdomen, however, if a subject does not tolerate administration into the abdomen, alternative sites may be selected (e.g. thigh or upper arm). Research nurses or other appropriately qualified research personnel will administer the SC

infusions at site visits, subjects may also self-administer the SC infusions after receiving appropriate training by a research nurse or other study personnel. The infusions will be administered at the clinical site on those days when a clinic visit occurs and off-site at the subject's home, workplace, or other location convenient to the subject by a trained study nurse or will be self-administered by the subject and/or caregiver on all other days.

Subjects should be instructed to take their APL-2 treatment as prescribed, and to contact the investigator immediately for guidance in the event of any missed doses. In subjects with PNH, it has been observed that discontinuation of APL-2 or noncompliance with the prescribed dose regimen may lead to the potential for an increased risk for serious hemolysis. The Sponsor's medical monitor should be contacted before interrupting or discontinuing treatment with APL-2.

Dosing records will be maintained at the clinical site and available for review by the Sponsor.

11.3.4 Dose Escalation, Additional Dose Levels

Dose escalation from 270 mg/d to 360 mg/d, or de-escalation from 360 mg/d to 270 mg/d may occur, and additional dose levels but not exceeding 360 mg/d may be added, as determined by the SMC.

11.4 Concomitant Medications

11.4.1 Prophylactic Antibiotics

Prophylactic antibiotic therapy will be prescribed to all subjects to minimize potential infection risk. Prophylactic antibiotics will generally be initiated on Day 1 before initiation of APL-2 dosing and continue throughout the dosing period until 2 weeks after the last dose. However, for patients receiving prophylactic erythromycin or azithromycin prophylactic antibiotics will be initiated at least one week prior to the first dose of APL-2, and QTc interval confirmed prior to dosing with APL-2.

11.4.1.1 Primary Prophylactic Antibiotic

- Penicillin V 500 mg twice daily

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on beta-lactam antibiotic (e.g. penicillin, amoxicillin, etc.) therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity. Before initiating therapy with penicillin V, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins or cephalosporins. If subjects have a known hypersensitivity to penicillin/amoxicillin they may be prescribed an alternative antibiotic at the outset.

Other frequently reported adverse effects in patients taking penicillin are diarrhea/loose stools, nausea, skin rashes and urticaria, and vomiting. Patients should, therefore, be advised that these reactions may occur.

11.4.1.2 Alternative Prophylactic Antibiotics

- Erythromycin 500 mg twice daily or Azithromycin 500 mg 3 times per week

Erythromycin 500 mg twice daily, or Azithromycin 500 mg 3 times per week may be considered as a suitable alternative in subjects who are unable to tolerate penicillin.

Treatment should be switched to another alternative antibiotic if there is evidence of penicillin or erythromycin-related tolerability issue (such as nausea and diarrhea). The PI will discuss and agree to a suitable alternative with the Sponsor's medical monitor. The agreement will be noted in the subject's medical records.

11.4.2 Rescue Antibiotics

Body temperature and vital signs will be monitored at the clinical site and relevant blood parameters monitored regularly throughout the study to assess for signs of infection. The PI should be contacted immediately in the event of a suspected infection despite prophylactic antibiotic treatment for guidance and appropriate action to be taken. Action to be taken may include administration of a broad-spectrum antibiotic to cover possible resistant organisms such as resistant pneumococcus (e.g. levofloxacin).

11.4.3 Iron Supplements

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

12. STUDY PROCEDURES

Please see the Study Flow Chart for Part A in Section 3 for a summary of the schedule of study participation and procedures through the Core Study Phase (Screening to Day 336). A summary of the schedule of study participation and procedures for the Part B Long-Term Extension Phase is provided in Section 17.3.2, Table 4.

The schedule of visit dates should be established, prior to, or at the time of screening allowing subjects an opportunity to assess whether there are likely to be significant conflicts with other activities or planned absences. To the extent possible, subjects will be expected to adhere to the visit schedule and any re-scheduling of visits must be agreed, in advance, with the PI and Sponsor to ensure that the dosing of study medication can continue daily as required.

Please Note: Subjects are allowed to utilize alternate study sites through the course of the study, if necessary to adhere to the visit schedule.

12.1 Screening

Screening will begin within 30 days prior to dosing to confirm that subjects meet the subject selection criteria for the study. Informed consent will be obtained at screening (see Section 15.6.3). Subjects will have to meet all eligibility criteria before being enrolled into the study (see Section 10).

Subjects should not be rescreened once they have been designated as a screen failure, unless this is discussed in advance and documented in writing with the sponsor.

The following will be recorded at screening: ECG, vital signs, hematology, serum chemistry, urinalysis, serum pregnancy test, physical examination, medical history, including concomitant medications, and demographic data, including, sex, age, race, body weight (kg), height (cm).

Confirm sufficient supplementation of iron, folic acid and vitamin B12 prior to treatment phase, if not, subjects need to be treated with supplements for at least 3 weeks prior to study enrollment.

Medical history on hemoglobin level, and the number of RBC transfusions in the past year prior to study enrollment will be collected.

Treatment history of dose and duration will be collected such as steroids, and rituximab.

Subjects requiring alternative prophylactic antibiotics (Erythromycin 500 mg twice daily, or Azithromycin 500 mg 3 times per week) will initiate antibiotic treatment at least one week prior to first dose of APL-2. QTc interval is to be confirmed prior to dosing with APL-2.

Screening procedures are listed in the Study Flow Chart in Section 3.

12.2 Vaccination Period (Day -30 to Day 1)

Subjects will be administered vaccinations unless there is documented evidence of having received vaccination against the following within 2 years of screening:

- *Neisseria meningitides* type A, C, W, Y and type B (administered as two separate vaccinations)
- *Streptococcus pneumoniae* (with a pneumococcal conjugate or pneumococcal polysaccharide [PCV13 or PPSV23] vaccine)
- *Haemophilus influenza Type B* (Hib vaccine)

For subjects who do not have documented evidence of receiving the above vaccinations within 2 years prior to screening, vaccinations may be administered during screening, up to Day 1, prior to dosing with APL-2 (along with boosters administered during the study, if required).

Vaccination is mandatory unless documented evidence exists that subjects are non-responders to vaccination as evidenced by titers or display titer levels within acceptable local limits. The PI will discuss with the Sponsor in regard to individual patient circumstances.

For subjects requiring vaccination, the following procedures should be followed:

***Neisseria meningitides* type A, C, W, Y and type B**

The initial vaccination must be administered during screening up to Day 1, prior to dosing with APL-2. This will be followed by a booster for *Neisseria meningitides* (both vaccines) after at least 8 weeks (Day 56).

***Streptococcus pneumoniae* (PCV13 and PPSV23 vaccine)**

If the subject requires *streptococcus pneumoniae* vaccination, the subject will be administered the PCV13 vaccine during the screening period (up to Day 1, prior to dosing), followed by a booster PPSV23 vaccine administered at least after 8 weeks (day 56).

Haemophilus influenza Type B (Hib vaccine)

If the subject requires vaccination for *Haemophilus influenza Type B* (Hib), the vaccination must be administered prior to Day 1 APL-2 dosing.

12.3 Baseline (Day 1)

Confirm subjects meet all eligibility criteria prior to dosing. Baseline vital signs, laboratory tests, urine sample, triplicate 12-lead ECG, urine pregnancy test, concomitant medications, adverse events, and FACIT and LASA assessments will be collected. Subjects will receive a SC dose of APL-2, and injection site assessment will be performed. Preventative antibiotics will be prescribed for use during treatment.

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

12.4 Treatment Period (Day 1 to Day 336)

Subjects will receive daily SC doses of APL-2 on Days 1 through Day 336. APL-2 will be administered at the clinical site by study personnel or off-site at the subject's home, workplace, or other location convenient to the subject by a trained study nurse or will be self-administered by the subject and/or caregiver.

Specific procedures for each visit are listed in the Study Flow Chart in Section 3.

12.4.1 On Site Administration

The first 3 daily SC doses of APL-2 (Day 1 through Day 3) as well as doses on 7, 14 and 28, 56, 84, 112, 140, 168, 224, 280, and 336 will be administered at the clinical site. Subjects will remain in the clinic for at least 4 hours after receiving the first dose of APL-2 on Day 1.

Triplicate 12-lead ECG, blood and urine samples for laboratory analysis, PK/PD, and antigenicity will be taken during site visits as outlined in the Study Flow Chart in Section 3.

12.4.2 Outpatient Administration (Day 4 to Day 336)

From Day 4 through Day 336 daily doses of APL-2 will be administered off-site by a trained 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 clinical site visit days (see above). Home nursing is an optional service and is not required if subject can properly self-administer APL-2. Home nursing may be started/re-started if subject requires additional training on self-administration.

Subject, caregiver, and/or nurse is to report adverse events and concomitant medications to the clinical site.

Note: Study Procedures for Visit 15 (Day 336) may be different for subjects that elect to enter the Part B Long-Term Extension Phase. These subjects may initiate a different dose regimen of APL-2 and will be dispensed drug for home administration. If a subject is to enter the Part B Long-Term Extension Phase and it is confirmed that the subject will initiate the APL-2 dose regimen intended for use during the Long-Term Extension Phase (APL-2 1,080 mg twice weekly), the subject should be instructed to skip their Core Study Phase dose the day before Visit 15. Subjects that will not initiate a new dose at Visit 15 should take their regular Part A Core Study Phase daily dose through Visit 15.

Section 17.3 provides details on the Long-Term Extension Phase.

12.5 Part B: Long-Term Extension Phase (Day 336 and Beyond)

At Visit 15 (Day 336; Week 48) subjects may elect to enter the Part B Long-Term Extension Phase in order to continue to receive treatment with APL-2 indefinitely until the subject discontinues or the APL-2 development program is terminated. Subjects that elect to enter the Long-Term Extension Phase should complete study procedures as outlined in Section 17.3 and Table 4. These subjects may initiate a different dose regimen of APL-2 and will be dispensed drug for home administration.

12.6 Follow-up/ Early Termination Follow-up (ETFU)

All subjects that complete study treatment through Day 336 that do not elect to enter the Part B Long-Term Extension Phase will be asked to return to the clinical site for a follow-up visit on Day 378.

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.

Specific procedures including blood and urine collections for laboratory analysis, PK/PD and antigenicity for each visit are listed in the Study Flow Chart in Section 3.

12.6.1 Exit Visit / Early Termination (ET) Visit

All subjects will be asked to return to the clinical site for the Exit Visit, 12 weeks after the final dose of APL-2.

Study participation for each subject will be concluded following completion of the Exit Visit. Subjects that complete Part A and do not elect to enter Part B the study will return to the clinical site for an Exit Visit on Day 420.

If a subject withdraws from the study prior to the scheduled Exit Visit, all Exit Visit evaluations should be performed at the subject's final visit to the clinic, including the collection of blood samples for PK and/or PD assessments, as well as a post-dose antigenicity sample if not yet collected.

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

12.6.2 Unscheduled Follow-up Visits

All subjects will be asked to return to the clinical site for additional follow-up visits if considered necessary by the PI or if the PK/PD sampling schedule is modified or extended based on interim results.

Unscheduled follow-up visits may include any of the procedures listed in the Study Flow Chart in Section 3.

12.6.3 Scheduled End of Study

The end of the Part A Core Study Phase is scheduled after completion of the Exit Visit evaluations in the 2 cohorts. The clinical conduct of the study for subjects that do not elect to enter the Part B Long-Term Extension Phase is intended to last approximately 15 months, including screening. Subjects that enter the Part B Long-Term Extension Phase will continue to receive treatment with APL-2 indefinitely until the subject discontinues or the APL-2 development program is terminated.

This time period may change in the event that the study is terminated early, additional dose groups are enrolled, additional time is required to review safety between dose groups, extended safety and PK sampling is added for a dose group (e.g., extended beyond Day 420), or a decision is made to complete an unscheduled analysis between dose groups.

12.7 Dose Escalation or De-escalation and Periodic Safety Review

Through the Part A Core Study Phase (up to Day 336), dose escalation will never exceed 360 mg/d without approval from the SMC and the IRB. Decisions to dose escalation or de-escalation

between the two dose groups may be made by the Sponsor. Review of doses above 360 mg/d will be comprised of SMC and IRB approval examination of all cumulative safety, tolerability and efficacy data (e.g., physical examinations, ECGs, vital signs, clinical laboratory tests, and adverse events) and a thorough assessment of all safety data will occur prior to initiation. PK/PD data and predicted exposure for subsequent doses based on emerging PK data will also be reviewed prior to determining the proposed dose adjustment.

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

12.7.1 Safety Monitoring Committee

A Safety Monitoring Committee (SMC) will have the responsibility to conduct a thorough safety assessment at regular intervals during the treatment phase of the study. A key responsibility of the SMC will be to decide whether to continue or modify the study based on recommendations by the Sponsor and upon an evaluation of emerging safety data. The SMC will comprise at a minimum of the PIs with active and enrolled subjects, a Sponsor representative, an AIHA expert not involved in the study and an Infectious Disease Specialist.

The first SMC meeting will be scheduled once four enrolled subjects complete 28 days of dosing or at an earlier time point in order to review subject data, and subsequent SMC meetings will be held on an every 6-month interval throughout the study. An *ad hoc* SMC data reviews may be recommended by the SMC or requested by the Sponsor at any time during the study.

If efficacious and safe, APL-2 may improve Hb levels, reduce reticulocyte counts, and reduce transfusion dependency in these patients. The SMC may, in consultation with the PI and Sponsor, be responsible for reviewing individual subject data to understand if there is a health benefit in these individuals at any time during the treatment period. If a benefit is observed the SMC may recommend extending the treatment beyond 336 days through a protocol amendment.

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

12.8 Treatment Discontinuation and Study Withdrawal

Subject participation in this trial may be discontinued and subjects may be withdrawn from study for any of the following reasons:

1. Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the PI that continued participation is not in the best interest of the subject.
2. Subject's decision to withdraw.
3. Subject failure to comply with protocol requirements or study-related procedures.
4. Termination of the study by the Sponsor, FDA, or other regulatory authorities.

The reason for treatment discontinuation and withdrawal from the study must be recorded in the subject's CRF.

If a subject is withdrawn from the trial prior to study completion, the subject will undergo all procedures scheduled for ETFU and ET as the situation allows. Any subject withdrawn due to an

AE (whether serious or non-serious) or clinically significant abnormal laboratory test values will be evaluated by the PI or a monitoring physician and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the PI.

Apellis may determine to replace subjects who have withdrawn, even if replacement would bring total enrollment above planned numbers.

13. ASSESSMENTS

13.1 Assessments

Assessments to be performed during the study are described below. Every effort should be made to ensure that the protocol-required assessments are completed as described.

If deemed necessary, additional safety measurements will be performed at the discretion of the PI.

13.1.1 Body Height and Weight

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

13.1.2 Physical Examination

All physical examinations will include, at a minimum, assessment of the following: general, head, ears, eyes, nose and throat, dentition, thyroid (endocrine), heart, chest, lungs, abdomen, skin, extremities, back/neck, musculoskeletal, and lymph nodes.

A licensed physician or other licensed health care provider employed at the study site will examine each subject as outlined in the Study Flow Chart in Section 3.

Medical history will be recorded at screening. Hemoglobin level and number of RBC transfusions in the past year prior to study enrollment will be collected.

A symptom-driven physical examination may be performed at various unscheduled time points if deemed necessary by the PI.

13.1.3 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate will be measured before dosing, as outlined in the Study Flow Chart in Section 3.

Vital signs may be taken at any other times, if deemed necessary. Blood pressure and heart rate measurements will be performed with subjects in a seated position after resting for 5 minutes, except when they are supine or semi-reclined because of study procedures and/or AEs (e.g., nausea, dizziness) or if deemed necessary by the PI.

Vital signs will be measured before venipuncture and ECG assessment.

On the days that APL-2 is administered at the clinical site, vital signs will be measured pre- and post-dose.

13.1.4 Electrocardiogram Monitoring

Triplicate 12-lead ECGs will be measured digitally at the time points outlined in the Study Flow Chart in Section 3 with three readings taken at least one minute and no more than 2 minutes

apart. ECGs will be taken following resting in the supine position for 10 minutes in a quiet environment and prior to APL-2 dosing and any blood sampling procedures.

ECGs will be assessed, interpreted and signed and dated by the PI or suitably qualified delegate. The ECGs will be classified as normal, having a not clinically significant (NCS) abnormality, or having a clinically significant (CS) abnormality. In addition, ECG parameters of ventricular rate, PR interval, QRS duration, and QT interval (corrected using both Bazett's and Fridericia's method, and uncorrected) will be reviewed for eligibility and ongoing safety.

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

The FACIT Fatigue Scale is a 13 item Likert scaled instrument which is self-administered by the subjects during clinic visits as outlined in the Study Flow Chart in Section 3. 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, some responses are reversed to ensure that the higher score corresponds to a higher quality of life. The FACIT Fatigue Scale and scoring guidelines are provided in the Manual of Procedures (MOP) (see Appendix 17.1).

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

The Linear Analog Scale assessment (LASA), which consists of five single statements asking respondents to rate, on zero to ten scales, their perceived level of functioning (see Appendix 17.2). This LASA scale has since been utilized in multiple trials. LASA is self-administered by the subjects during clinic visits on as outlined in the Study Flow Chart in Section 3.

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 QoL is also included. The Likert scales run from 0 (as bad as it can be) to 10 (as good as it can be). Thus, higher ratings suggest higher QoL.

The LASA is a psychometrically-validated brief measure of QoL. Despite its brevity, it provides an overall estimate and covers four major subcomponents of QoL (physical, emotional, spiritual, and intellectual). It therefore gives a global, comprehensive view of a patient's QoL (Locke, 2007).

13.1.7 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Study Flow Chart in Section 3. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI or recommended by the SMC. The clinical laboratory tests include (but are not limited to) the following:

13.1.7.1 Hematology

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

13.1.7.2 Coagulation

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

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

13.1.7.3 Serum Chemistry

- Blood urea nitrogen (BUN)
- Creatinine
- Estimated creatinine clearance (using Cockcroft-Gault formula) –screening only
- Bilirubin (total, direct, indirect)
- Albumin
- Alkaline phosphatase (ALP)
- Lactate dehydrogenase (LD)
- Haptoglobin
- Gamma-glutamyl transpeptidase (GGT)
- Calcium
- Creatine kinase (CK)
- Aspartate aminotransferase (AST)
- Alanine Aminotransferase (ALT)
- Uric acid
- Glucose
- Sodium
- Potassium
- Chloride
- Ferritin
- B12/folate
- Phosphate

13.1.7.4 Urinalysis

- pH
- Specific gravity
- Protein
- Glucose
- Ketones
- Bilirubin
- Blood
- Nitrite
- Urobilinogen
- Leukocyte esterase

If an abnormality is noted for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination will be performed.

13.1.7.5 Human Chorionic Gonadotropin (Serum Pregnancy Test), Urine Pregnancy Test, Follicle-Stimulating Hormone

Serum Pregnancy Test and Urine Pregnancy Test will be performed for females only. Follicle-Stimulating Hormone (FSH) will be performed for postmenopausal females at screening only.

13.1.7.6 AIHA Experimental Labs

- DAT monospecific IgG
- DAT monospecific C3
- Immunoglobulins Quantitative (IgG, IgM and IgA)
- Serum Cold Agglutinin Titer (at 4C) [for CAD subjects only]

13.1.8 Injection Site Assessment

On the days of clinical visits, an assessment of the APL-2 injection site will be performed within 30 minutes after study drug administration infusion is complete. The assessment will be performed by a physician or other licensed health care provider (i.e. study nurse) as delegated by the PI. The injection site and the surrounding area will be inspected for redness, swelling, induration, and bruising; and the subject will be asked about the presence of pain and/or tenderness. The date, time, and outcome of the injection site assessment will be recorded on the source documents and CRFs.

Subjects will be trained to notify the PI or other study personnel in the event that an injection site reaction occurs after self-administration of APL-2. All CS findings will be recorded as AEs.

13.2 Pharmacokinetic Assessments

13.2.1 Blood Sampling and Processing

Blood samples for PK assessment of APL-2 will be collected via direct venipuncture at the time points delineated in the Study Flow Chart in Section 3.

On Day 1 only, a PK sample will be taken pre-dose and at a minimum of 4 hours post-dose (or later depending on how long the subject is kept at the clinic). All PK samples on other study days will be collected pre-dose.

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

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

13.2.2 Analytical Method

Serum sample analysis will be performed using GLP-compliant validated procedures and methods. The methods used and the results obtained will be included in the final report as an appendix.

13.3 Pharmacodynamic Assessments

Blood samples will be collected via direct venipuncture at the time points delineated in the Study Flow Chart in Section 3 for PD assessment of complement activation through the classical (e.g., CH50) and alternative (e.g., AH50) pathways, and C3 deposition on RBCs. Blood samples will also be collected to measure C3 levels. Other relevant PD markers may also be assessed.

Preliminary PD analysis may be performed to reconsider sampling time points as the study progresses or to guide the dose escalation decision.

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

13.4 Anti – APL-2 Antibody Assessments

Blood samples for anti-APL-2 antibody assay will be collected via direct venipuncture at the time points delineated in the Study Flow Chart in Section 3.

For subjects with positive anti-APL-2 antibody in last dose samples, additional samples of 6 and 12-month from last dose will be collected for further assessments.

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

13.5 Blood Volume for Study Assessments

Table 3: Blood Volume during Study (Part A; up to Day 420)

Assay	of Time Points	Approximate Volume per Time Point (mL)	Approximate Sample Volume Over Course of Study (mL)
Pharmacokinetics	15	2	30
Anti-APL-2 Ab assay	14	5	70
Hematology	15	4	60
Chemistry	15	5	75
Screen Pregnancy	1	N/A – tested from Chemistry sample	N/A – tested from Chemistry sample
Coagulation profile	8	7	56
Complement profile (C3, CH50 and AH50)	14	3	42
Flow cytometry for C3 deposition	14	4	56
Plasma Hb	14	3	42
Haptoglobin Ferritin, Vit B12, Folate	15	5	75
DAT monospecific IgG and C3	15	4	60
Immunoglobulin Quantitative (IgG, IgM and IgA) and Serum Cold Agglutinin Titer	15	10	150
		Total Approximate Blood Volume For Study	**716 ***

* Represents the standard collection volume planned over the duration of the study, actual volume may vary.

For subjects that enter the Part B Long-Term Extension Phase, the volumes noted above will continue to be collected as noted in the Study Flow Chart for the Part B Long-Term Extension Phase (Table 4).

13.6 Pregnancy Tests

For WOCBP, a serum pregnancy test will be performed at screening, and subjects with a positive test will be excluded from the study. A follow up urine pregnancy test will be performed on Day 1 pre-dose (a negative urine pregnancy test must be received before dosing with study drug). A urine pregnancy test will also be performed at each site visit (pre-dose) if applicable. A final urine pregnancy test will be performed at the final Exit Visit. Male subjects will be counseled to avoid donating sperm during the time between the first dose on Day 1 and the 90 days after their last dose.

14. ADVERSE EVENTS

14.1 Definition

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign, including a clinically significant abnormal laboratory finding, symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug (United States Food and Drug Administration (FDA) guidance, December 2012). Any abnormal laboratory finding that is deemed not clinically significant is not an AE.

Adverse events include the onset of new illness and the exacerbation of pre-existing conditions. Any medical condition that is present at the time that the subject is screened should be recorded on the medical history eCRF and not reported as an AE. However, if that condition deteriorates or severity changes at any time during the study, it should be recorded as an AE.

Any AEs that occur prior to dosing on Day 1 will be categorized as pre-treatment events. TEAEs will be 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.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

14.2 Recording Adverse Events

All AEs encountered during the study will be monitored and reported in detail in the source documents and documented on the eCRF, from signing of the ICF until the Exit Visit. AEs, especially those for which the relationship to study drug is considered by the PI to be possibly or probably related, should be followed up until they have returned to the baseline status or stabilized. If a clear explanation is established, it should be recorded on the eCRF.

Subjects will be monitored throughout the study for adverse reactions to the study formulations and/or procedures.

AEs (whether serious or non-serious) including clinically significant abnormal laboratory test value(s) will be evaluated by the PI and treated and/or followed up until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI.

If required, treatment of SAEs will be performed by a physician, either at the Study Site or at a nearby hospital emergency room. When appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as recovered/resolved, recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved, fatal, or unknown.

14.3 Treatment and Follow-up of Adverse Events

AEs (whether serious or non-serious), including clinically significant abnormal laboratory test values, will be evaluated by the Investigator and treated and/or followed up until the symptoms or value(s) return to baseline or are clinically stable. Treatment of AEs will be performed by appropriately trained medical personnel, either at the Study Site or at a nearby hospital emergency room. When appropriate, medical tests and/or examinations will be performed to document resolution of the event(s).

AEs continuing after completion of the study will be followed up by telephone or with visits per the discretion of the Investigator. If possible, the outcome of any AE that caused discontinuation from the study or was present at the end of the study should be reported, particularly if the AE was considered by the PI to be related to the study drug.

14.4 Reporting

The collection of clinical information will begin after the subject's written consent to participate in the study has been obtained. AEs will be collected after signing the ICF through to completion of the Exit Visit. Any events that occur prior to dosing on Day 1 will be categorized as pre-treatment events. Events occurring after dosing on Day 1 will be recorded as TEAEs. AEs may be either spontaneously reported or elicited during questioning and examination of a subject.

All identified AEs, including clinically significant laboratory findings, must be recorded and described on the appropriate AE or SAE page of the eCRF. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. AEs will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA®) coding dictionary.

Subjects experiencing AEs that cause interruption or discontinuation of study drug, or those experiencing AEs that are present at the Exit Visit should receive follow-up as appropriate. If possible, the outcome of any AE that caused permanent discontinuation or was present at the end of the study should be reported, particularly if the AE was considered by the PI to be related to the study drug.

14.4.1 Relationship of Events to Study Treatment

All AEs that occurred during this study will be recorded. The PI will review each event and assess its relationship to study drug treatment (definitely related, possibly related, unlikely related, not related, unknown). The date and time of onset, time relationship to drug dosing, duration, and outcome (recovered/resolved, recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved, fatal, or unknown) of each event will be noted.

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

Definitely Related	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (ie, an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Possibly Related	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely Related	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Not Related	• Event or laboratory test abnormality, is plausibly related to the participant's clinical state, underlying disease, or the study procedure/conditions • Time relationship to drug intake makes a relationship unreasonable • Other obvious causes for event or laboratory test abnormality exist
Unknown	• Report suggests an AE, however, cannot be judged at this time because information is insufficient or contradictory • More data for proper assessment is needed, or additional data is under examination

14.4.2 Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate	Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*.
Severe	Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**. Note: An experience may be severe but may not be serious, e.g., severe headache).

A semi-colon indicates 'or' within the description of the grade.
Note: Activities of Daily Living (ADL)
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

14.5 Serious Adverse Events

If any AEs are serious, special procedures will be followed. All SAEs will be reported to the Safety Monitor by the PI via fax or email within 24 hours of becoming aware of the event, whether or not the serious events are deemed drug-related. SAE reporting contact information will be provided separately and as included in the Safety Monitoring Plan. All SAEs must be reported to the applicable ethics committee by the PI in accordance with their regulations.

An SAE is any adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening is defined as an AE or suspected adverse reaction in the view of either the investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Unexpected is defined as an AE or suspected adverse reaction that is not listed in the IB or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

14.6 Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical concern specific to the Sponsor's product or program where ongoing monitoring and rapid communication by the PI to the Sponsor may be appropriate. These adverse events may be serious or non-serious. Applicable adverse events may require further investigation in order to characterize and understand, and depending upon the nature of the event, rapid communication by the trial Sponsor to other parties may also be required. These adverse events of special interest must be reported promptly to the sponsor. The adverse events of special interest include the following:

- Local or systemic infection of any origin
- Clinically significant decrease in kidney function
- Injection site reactions

- Thrombotic events

If an AESI occurs in a study subject, the study subject will be followed for resolution of the adverse event. A decision will be made by the Sponsor concerning further exposure to the study treatment and further participation in the study.

14.7 Unexpected Adverse Events or Unexpected Suspected Adverse Reactions

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of increased severity) if the IB referred only to elevated hepatic enzymes or hepatitis.

The Sponsor will be responsible for reporting any serious and unexpected adverse events to the applicable regulatory agencies as required.

14.8 Treatment and Follow up of Adverse Events

AEs (whether serious or non-serious), including clinically significant abnormal laboratory test values, will be evaluated by the Investigator and treated and/or followed up until the symptoms or value(s) return to baseline or are clinically stable. Treatment of AEs will be performed by appropriately trained medical personnel, either at the clinical site or at a nearby hospital emergency room. When appropriate, medical tests and/or examinations will be performed to document resolution of the event(s).

AEs continuing after completion of the study will be followed up by telephone or with visits per the discretion of the PI. If possible, the outcome of any AE that caused discontinuation from the study or was present at the end of the study should be reported, particularly if the AE was considered by the PI to be related to the study drug.

14.9 Pregnancy

Although pregnancy is not considered an AE, the outcome of a pregnancy, if there is a spontaneous abortion, congenital anomaly or other adverse fetal outcome, may be an SAE. All SAEs are to be reported to the study Sponsor on the SAE Reporting Form.

WOCBP and males with female partners of child-bearing potential will be instructed to practice an acceptable method of birth control (as defined in Section 10.1.1) for the duration of the study and 90 days after their last dose of study drug.

If a female subject or partner of a male subject becomes pregnant during the study, the PI should report the pregnancy to the Safety Monitor within 24 hours of being notified using the pregnancy report form. The subject or partner should be followed by the PI until completion of the pregnancy. At the completion of the pregnancy, the PI will document and report the outcome. If the outcome of the pregnancy meets the criteria for classification as an SAE (i.e.

postpartum complication, stillbirth, neonatal death, or congenital anomaly) the PI should follow the procedures for reporting an SAE (Section 14.4).

15. STATISTICS

15.1 Sample Size Justification

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

15.2 Statistical Analysis Methodology

A formal Statistical Analysis Plan (SAP) will be developed and finalized prior to locking the database. The full details of data presentations and analyses will be provided therein. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and included in the SAP. Any deviations from the final analysis plan or from what is outlined in the protocol will be discussed in the final study report.

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

15.2.1 Analysis Populations

15.2.1.1 Screened Population

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

15.2.1.2 Safety Population/ Intent-to-Treat (ITT) Population

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

15.2.1.3 Pharmacokinetic (PK) Population

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

15.2.1.4 Pharmacodynamic (PD) Population

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

15.2.1.5 Data Review for Analysis Populations

After all the data have been verified/coded/entered into the database, a review will be performed. The purpose of this review will be to define the analysis populations. The review will also check the quality of the data, identifying outliers, and making decisions on how to deal with problems in any data (e.g., missing values, withdrawals, protocol deviations). After the

pre-analysis review, resolution of all issues and documentation of all decisions, the database will be locked.

15.2.2 Safety Analyses

All safety endpoints will be evaluated using the Safety Population.

15.2.2.1 Adverse Events

Treatment emergent adverse events are defined as those AEs that develop or worsen after the first dose of study medication and up to 30 days beyond the last dose of study medication. The current version of MedDRA will be used to classify all AEs.

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

15.2.2.2 Clinical Laboratory Tests

A by-subject listing will be provided including changes from baseline. Laboratory values that are outside the laboratory reference range will be flagged.

15.2.2.3 Vital Signs and ECGs

Observed and change from baseline values for vital sign and ECG parameters will be listed.

Values of potential clinical significance (e.g. change in QTcF ≥30ms from baseline) will be flagged and summarized by study visit.

15.2.3 Efficacy Analyses

The efficacy endpoints will be evaluated for the ITT Population.

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

15.2.4 Pharmacokinetic Analyses

The PK parameters will be evaluated using the PK Population.

Individual concentration over time profile plots will be presented, with each cohort and dose group being identifiable. Both linear-linear and linear-log plots will be presented.

Where appropriate, steady-state PK parameters for APL-2 will be estimated from the individual serum concentrations over-time data, using actual sample times using a non-compartmental approach. Detailed PK analyses will include in the SAP.

15.2.5 Pharmacodynamic Analyses

The PD parameters will be evaluated using the PD Population.

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

15.2.6 Handling of Dropouts and/or Missing Data

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

Where appropriate screening values may be used as baseline in the event of missing Day 1 measurements.

Missing dates/times will be reviewed on a case by case basis for potential imputations, but the original data will always be presented in data listings.

15.2.7 Other Data Analyses

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

15.3 Interim Analyses

One interim analysis is planed 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.

15.4 Direct Access to Source Data/Documents

The PI must maintain, at all times, the primary records (i.e. source documents) of each subject's data for data verification. Examples of source documents are medical records, laboratory reports, study drug records, and eCRFs that are used as the source.

The PI will permit trial-related monitoring, audits, and inspections by the Sponsor and/or its' designee, IRB/IEC, and the regulatory agencies at any time during the study. The PI will ensure that the auditor is allowed direct access to the source data, medical records, eCRFs, and the Site's regulatory file for the study and any other pertinent information.

15.5 Quality Control and Quality Assurance

This study is to be performed in full compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements. The PI, Sponsor and/or its' designee are responsible for ensuring that the study staff receive appropriate training on the protocol, study procedures and any other relevant information.

Quality assurance and quality control systems are implemented and maintained using written Investigative site, Sponsor and/or designee Standard Operating Procedures (SOPs) to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s) and local laws, rules, regulations.

Quality control (QC) checks will be applied at each stage of data handling (e.g. edit checks) to ensure that all data are reliable and have been processed correctly.

15.5.1 Monitoring

On-site monitoring will be performed by the Sponsor's designee for the duration of the study. The monitor will ensure that the study is conducted, recorded and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirements. The monitor will verify the accuracy and completeness of the eCRF entries, source documents, and other study-related records against each other. The PI will provide direct access to source data/documents for study-related monitoring. It is important that the PI and the staff are available at these visits. The monitor will record the date of each visit together with a summary of the status and progress of the study. Proposed actions will be documented in writing to the PI.

15.6 Ethics

15.6.1 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, applicable regulations, the ethical princliples set forth in the Declaration of Helsinki, and the ICH Harmonized Tripartite Guidance for Good Clinical Practice, E6, R1 (ICH GCP).

15.6.2 Institutional Review Board/Ethic Committee

The study protocol, any amendments to the protocol, informed consent form, the Investigator's Brochure, and other study specific information will be reviewed and approved by the IRB/IEC. The study will not be initiated until the IRB/IEC has approved the protocol or a modification thereof. All records pertaining to IRB/IEC submission and approval should be kept in the site's regulatory files and Sponsor's Trial Master File (TMF).

The IRB/IEC must be constituted and operate in accordance with all applicable regulatory requirements.

15.6.3 Subject Information and Consent

The PI or appropriate designee is responsible for obtaining an informed consent. A written informed consent, in compliance with ICH Guidance E6, must be obtained from each subject prior to screening and enrollment or performing any study related procedures.

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. The subject will be given sufficient time to consider the study's implications before deciding to participate in the study. The subject and/or legal guardian will be required to sign and date an Informed Consent Form (ICF) and will be

assured that they may withdraw from the study at any time without jeopardizing their medical care. The PI shall retain the original, signed informed consent for study participation in the subject's medical record and shall provide the subject and/or legal guardian with a copy of the signed consent.

Patients that live outside the United States who may wish to participate in this study for a period of time within the United States will be pre-consented by the PI and the local physician. The ICF (in local language) will be emailed to the subject's local physician. The ICF will be provided in advance to the patients to ensure adequate time is provided to ask questions and discuss any concerns. This procedure is completed to ensure patients understand the study, procedures, risks, and benefits, etc., before traveling to the United States for a screening visit. The patient will be consented by the PI over the phone/video with the local physician present on the call/video to aid in the discussion. Additional trained translators will be provided if needed to ensure subjects fully understand the protocol and can ask questions. The ICF will be signed by the patient, local physician, and PI once the patient arrives in the United States for the screening visit. The executed ICF will be stored locally at the PI's office. The PI may wish to re-consent the patient again once arriving to the United States.

If there are any changes/amendments to the approved protocol, which may directly affect the subject's decision to continue participation in the study, the ICF shall be amended to incorporate the changes to the protocol and the subject must re-sign the IRB/IEC approved amended ICF.

15.6.4 Confidentiality

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

15.6.5 ClinicalTrials.gov

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

15.6.6 Termination of Study

The Sponsor reserves the right to suspend or discontinue this study for administrative and/or safety reasons at any time. The PI reserves the right to discontinue dosing subjects at any time for safety reasons.

15.7 Data Handling and Record Keeping

The PI must maintain all documentation related to this study. All essential documents (as defined in the ICH Guideline E6) and the data generated in connection with this study, together with the original copy of the final report, will be retained for at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor.

It is the responsibility of the Sponsor to inform the PI/Institution as to when these documents no longer need to be retained.

15.8 Protocol Amendments

Amendments to the study protocol may occur as the study progresses. Amendment(s) will be approved and signed off in the same way as the protocol.

15.9 Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

15.10 Finance and Insurance

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

15.11 Publication Policy

The data generated for this study are considered confidential information and are the property of the Sponsor. All study information provided to the PI and Site personnel by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

After the completion of the study, the data may be reported at a scientific meeting and/or submitted for publication in a scientific journal with the prior written consent of the Sponsor. The Sponsor must be given at a minimum 30 days to review the materials to be presented at a scientific meeting and/or for publication in a scientific journal.

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