Protocol No: APL2-203

An 18-Month Phase Ib/II Multi-Center, Open Label Study to Evaluate the Safety of Intravitreal APL-2 Therapy in Patients with Neovascular Age-Related Macular Degeneration (AMD)

Phase: Ib/II

Protocol Version: Version 3.0

Date: 03 August 2018

INVESTIGATOR AGREEMENT

Long Title:	An 18-Month Phase Ib/II Multi-Center, Open Label Study to Evaluate the Safety of Intravitreal APL-2 Therapy in Patients with Neovascular Age-Related Macular Degeneration (AMD)
Short Title:	Furlong
Protocol Number/Version/ Date	APL2-203/Version 3.0/03Aug2018
Study Phase:	Phase Ib/II
Sponsor Name and Address:	Apellis Pharmaceuticals 6400 Westwind Way, Suite A Crestwood, KY 40014
Investigational Test Article:	APL-2
US IND#:	124784
Indication Studied:	Neovascular Age-Related Macular Degeneration
Investigator Agreement:	I have read the clinical study protocol described herein, recognize its confidentiality, and agree to conduct the described trial in compliance with Good Clinical Practices (GCP), the ethical principles contained within the Declaration of Helsinki, this protocol, and all applicable regulatory requirements.

Principal Investigator:

Name: _____

Signature: _____

Date: _____/_____/_____ (DD/MMM/YYYY)

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SUMMARY OF CHANGES FROM THE PREVIOUS VERSION

Amendment 1

Amendment Number **1.0**	**Amendment Date** **03 Jan 2018**
Description of Change	**Section(s) Affected by Change**
Change: Collection of genotyping samples has been removed due to the nature of the study being conducted and given the small sample size.	3. Synopsis (Secondary Endpoints) 4. Schedule of Events 8.2.2 Secondary Endpoints
Change: Best Corrected Visual Acuity has been added as an assessment at screening. This was an administrative error.	4. Schedule of Events
Change: Language regarding informed consent has been updated to reflect a more accurate representation of the consent process for this study.	14.5.3 Subject Information and Consent 11.1 Screening Visit 1

Amendment 2

Amendment Number **2.0**	**Amendment Date** **14 Mar 2018**
Description of Change	**Section(s) Affected by Change**
Change: The T-cell assay has been removed from the study.	3. Synopsis (Exploratory Endpoint) 4. Schedule of Events 8.2.4 Exploratory Endpoints 12.3 Treatment Period 12.3 Exploratory Assessments 12.5 Blood Volume for Study Assessments 14.2.2.4 Exploratory Endpoints
Change: The sample size has been increased by 10 subjects for a total of 20 subjects in the study.	3. Synopsis (Number of Planned Subjects, Sample Size) 8.3 Study Design 9. Subject Selection 14.1 Sample Size Justification
Change: The predose vital window has been amended from “approximately 1 hour before dosing” to “within 90 mimutes of dosing”, to accommodate the large number of predose assessments	4. Schedule of Events 11.3 Baseline Visit 11.4 Treatment Period 12.1.5 Vital Signs
Change: The inclusion criteria for a 50% reduction in excess macular fluid has been amended to a clinically meaningful reduction in excess macular fluid	3. Synopsis 9.1 Inclusion Criteria
Change: The requirement for a patient’s IOP to be +/-5 mmHg from baseline after Anti-VEGF injection has been amended to <21 mmHg for safety and consistency	8.3 Study Design 10.2.2 Dosing 10.5 Retreatment with Anti-VEGF 11.3 Baseline Visit

	12.1.9 Post-Injection Assessment
Change: The “Changes in number of Anti-VEGF injections” exploratory endpoint has been amended to “number of Ant-VEGF injections”for clarity	3. Synopsis 8.2.4 Exploratory Endpoints 14.2.2.4 Exploratory Endpoints

Amendment 3

Amendment Number 3.0	**Amendment Date: 7 August 2018**
Description of Change	**Section(s) Affected by Change**
Change in formulation of APL-2.	10.1. Identity of Investigational Product 10.2.3. Investigational Product Administration 10.3.2. Packaging 10.3.3. Storage
It was specified that: <u>All suspected cases of Endophthalmitis should be reported as a Serious Adverse Event.</u>	10.6.2 Endophthalmitis Treatment
The specification that a 50% reduction in macular fluid was the requirement for a “clinically meaningful” reduction was removed for consistency; this change was enacted for Amendment 2 of the protocol, but Section 11.2 was not updated. The error has been corrected in this amendment.	11.2 Screening Visit

1. SPONSOR INFORMATION

Sponsor

Apellis Pharmaceuticals, Inc.
6400 Westwind Way, Suite A
Crestwood, KY 40014
USA

Sponsor Representative

PPD

Tel.: PPD

E- PPD

Signature: _PPD_____

Date: __07__/__Aug__/__2018__ (DD/MMM/YYYY)

2. ABBREVIATIONS

ADA	*Anti-drug Antibodies*
AE	*Adverse Event*
AM	*APL-2 Monthly*
AMD	*Age-related Macular Degeneration*
ALT (SPGT)	*Alanine Aminotransferase*
AST (SGOT)	*Aspartate Aminotransferase*
AUC	*Area Under the Curve*
Ba	*Complement Component B, Fragment a*
BCVA	*Best Corrected Visual Acuity*
BQL	Below-Quantification-Level
BUN	*Blood urea nitrogen*
°C	*Degree Centigrade*
C3	*Complement component 3*
C3a	*Complement Component 3, Fragment a*
C3d	*Complement Component 3, Fragment d*
C5a	*Complement Component 5, Fragment a*
cc	*Cubic Centimeter*
CCP	*Complement Control Protein*
CEP	*ω-(2-carboxyethyl)pyrrole*
CFB	*Complement Factor B*
CFH	*Complement Factor H*
CFI	*Complement Factor I*
CFR	*US Code of Federal Regulations*
CH50	*Classical Pathway of Complement Functional Test*
CMV	*Cytomegalovirus*
C_{max}	*Maximum Observed Concentration*
CNV	*Choroidal neovascularization*
CRA	*Central Retinal Artery*
CRC	*Central Reading Center*
CRF (eCRF)	*Case Report Form (electronic CRF). (Used interchangeably)*
CRL	*Charles River Laboratory*

CRO	*Contract Research Organization*
CTCAE	*Common Terminology Criteria for Adverse Events*
C_{trough}	*Lowest Observed Concentration after a dose*
DA	*Disk Area*
DCFP	*Digital Color Fundus Photography*
DSMB	*Data Safety Monitoring Board*
EOM	*Every Other Month*
ERG	*Electroretinography*
ETDRS	*Early Treatment Diabetic Retinopathy Study*
FAF	*Fundus Autofluorescence*
FDA	*United States Food and Drug Administration*
FFA/FA	*Fundus Fluorescein Angiography or Fluorescein Angiography*
FSH	*Follicle-Stimulating Hormone*
G	*Gauge*
GA	*Geographic Atrophy*
GCP	*Good Clinical Practice*
GLP	*Good Laboratory Practices*
HCG	*Human Chorionic Gonadotropin*
hERG	*human ether-a-go-go gene*
HIPAA	*Health Insurance Portability and Accountability Act*
ICF	*Informed Consent Form*
ICH	*International Conference on Harmonization*
ICH M3(R2)	*International Conference on Harmonization Guideline M3 (R2)*
IEC	*Independent Ethics Committee*
IMP	*Investigational Medicinal Product*
IOP	*Intra Ocular Pressure*
IR	*Infrared Reflectance*
IRB	*Institutional Review Board*
IV	*Intravenous*
IVT	*Intravitreal*
IWR	*Interactive Web Response*
kDa	*Kilodalton*

kg	*Kilogram*
LFT	*Liver Function Test*
LH	*Luteinizing Hormone*
LL-BCVA	*Low luminance best corrected visual acuity*
LLD	*Low luminance deficit*
MAC	*Membrane Attack Complex*
MedDRA	*Medical Dictionary for Regulatory Activities*
mg	*Milligram*
MI	*Myocardial Infarction*
mITT	*Modified Intention to Treat*
mL	*Milliliter*
mmHg	*Millimeter Of Mercury*
MNV	*Macular Neovascularization*
MOP	*Manual of Procedures*
MTD	*Maximum Tolerated Dose*
NOAEL	*No Observable Adverse Effect Level*
NOEL	*No Observable Effect Level*
NL-BCVA	*Normal Luminance Best-Corrected Visual Acuity*
OCT	*Optical Coherence Tomography*
PD	*Pharmacodynamic*
PDT	*Photodynamic Therapy*
PEG	*Polyethylene Glycol*
PEG40	*Polyethylene Glycol (40 kDa nominal molecular weight)*
PI	*Principal Investigator. (PI and Investigator are used interchangeably)*
PK	*Pharmacokinetic*
PP	*Per Protocol*
QC	*Quality Control*
RBC	*Red Blood Cell*
RPE	*Retinal Pigment Epithelium*
SAE	*Serious Adverse Event*
SAP	*Statistical Analysis Plan*
SC	*Subcutaneous*

SC5b-9	*Soluble Terminal Complement Complex (i.e. soluble analog of MAC)*
SD-OCT	*Spectral Domain Optical Coherence Tomography*
SEOM	*Sham Every-Other-Month*
SM	*Sham Monthly*
SMC	*Safety Monitoring Committee*
SOP	*Standard Operating Procedures*
TEAE	*Treatment Emergent Adverse Event*
TK	*Toxicokinetic*
T_{max}	*Time to Maximum Measured Concentration*
TMF	*Trial Master File*
$t_{1/2}$	*Terminal Elimination Half-life*
VA	*Visual Acuity*
VEGF	*Vascular Endothelial Growth Factor*
µL	*Micro liter*
WBC	*White Blood Cell*
WOCBP	*Women of Child-Bearing Potential*
WONCBP	*Women of Non Child-Bearing Potential*
YAG	*Yttrium Aluminum Garnet*

3. SYNOPSIS

Protocol Number:

APL2-203

Protocol Title:

An 18 Month Phase Ib/II, Multi-Center, Open Label Study to Evaluate the Safety of Intravitreal APL-2 Therapy in Patients with Neovascular Age-Related Macular Degeneration (AMD)

Version Number:

Version 3.0

Investigational Product, Dose and Route of Administration:

- APL-2
- 15 mg/ 100 µL
- Intravitreal Injection

Study Phase and Type:

Phase Ib/II study consisting of an open-label, multicenter, non-randomized group

Number of Planned Subjects:

Open label arm, with approximately 20 patients with clinical diagnosis of neovascular AMD

Treatment Groups:

- Group 1: APL-2 15 mg/ 100 µL intravitreal injection

Duration of Study Participation:

The planned length of participation in the study for each subject is a maximum of approximately 19 months (76 weeks), including a one-month (4-week) screening period, 12-month (48-week) treatment period and 6-month (24-week) follow-up period.

Study Population:

Patients, at least 60 years of age, with neovascular AMD

Rationale for the Study:

APL-2 has proven safe and tolerable in a Phase I study in patients with wet AMD (protocol POT-CP043014; NCT02461771) and in a second Phase II study in subjects with Geographic Atrophy (GA) (protocol POT-CP121614; NCT02503332) associated with AMD. During the Phase II study, an imbalance in new exudation in subjects treated with APL-2 was discovered.PPD

PPD . It was noted that of the 20 APL-2-treated subjects with new study eye exudation, 14 subjects received APL-2 Monthly (AM) treatment and 6 subjects received Every Other Month (EOM) treatment. However, treatment with APL-2 was discontinued for these subjects after the onset.

Fourteen of the 21 (67%) subjects that developed new study eye exudation had a prior history of exudative AMD in the non-study fellow eye. No significant imbalance in history of exudative AMD in the fellow eye was observed among the three arms to explain the imbalance in new exudation observed in study eyes. Visual acuity (VA) data did not demonstrate clear differences between subjects developing new study eye exudation compared with those that did not.

Given these findings, further exploration is necessary to study the effects of APL-2 in subjects with neovascular AMD.

Study Objectives and Endpoints:

Objective

The objective of this study is to establish the safety and tolerability of intravitreally injected APL-2 in patients with neovascular AMD.

Endpoints

Primary Endpoint:

- Incidence and severity of ocular and systemic Treatment- Emergent Adverse Events (TEAEs)

Secondary Endpoints:

- Changes from baseline in physical examination findings and laboratory parameters
- Changes from baseline in central macular thickness on OCT over 12 months

Pharmacokinetic Endpoint:

- APL-2 pharmacokinetic concentrations

Exploratory Endpoint:

- Number of anti-Vascular Endothelial Growth Factor (anti-VEGF) PRN injections from Visit 4 to the Exit Visit (Visit 17)

Study Design:

This is an 18-Month Phase Ib/II, multi-center, open label study to assess the safety and tolerability of monthly IVT injections of APL-2 in subjects with neovascular AMD.

Patients diagnosed with AMD in the study eye, who are receiving an intravitreal anti-VEGF drug, and who meet all other inclusion/exclusion criteria will be included in the study. The study will include approximately 20 subjects across at least 3 U.S. sites.

Patients will initially be screened between Day -28 and prior to treatment on Day 1. Screening procedures will include laboratory tests, Best Corrected Visual Acuity (BCVA), ophthalmological exam, Intraocular Pressure (IOP), and Spectral Domain Optical Coherence Tomography (SD-OCT). Upon entry into the study (after signing the informed consent), subjects will be assigned a screening number. At screening visit 1 (Day -28) subjects will have an SD-OCT taken to assess for the presence of any subretinal, intraretinal, or sub-Retinal Pigment Epithelium (sub-RPE) fluid, followed by an IVT dose of an anti-VEGF drug. Subjects will return two weeks later for screening visit 2 (Day -14) and will have another OCT performed to confirm a decrease in excess fluid in the macula. Upon confirmation bu the Investigator of fluid reduction, subjects who meet all inclusion and exclusion criteria will be enrolled in the study and will return at Day 1 for treatment (Visit 3; Day 1). Treatment on Day 1 will entail a mandatory IVT dose of an anti-VEGF drug followed by an IVT injection of APL-2.

All subjects will receive monthly APL-2 injections for 12 months during their scheduled monthly treatment visits. At each treatment visit, safety assessments will be performed including vital signs, labs and urinalysis, and SD-OCT. BCVA, fundus examination, dilated indirect ophthalmoscopy and slit lamp examination will also be performed. Subjects will be assessed at each treatment visit for the need for retreatment with an anti-VEGF drug based on pre-specified retreatment criteria. During follow-up, safety assessments will be performed for all subjects at months 15 and 18. Subjects who discontinue study treatment, should be encouraged to continue participation in the study and return to the clinical site for their scheduled study procedures. Subjects who fully withdraw from the study before month 12, should complete the Termination Visit.

An external, independent Safety Monitoring Committee (SMC) will assess the progress and cumulative safety/tolerability data of the study.

Subjects who fail the screening procedures should not be re-screened for the study unless this is agreed in advance and documented in writing with the sponsor.

Inclusion Criteria:

Ocular- specific inclusion criteria apply to the **study eye** only.

1. Age $\geq$ 60 years.
2. Normal Luminance best corrected visual acuity (NL-BCVA) of 24 letters or better using Early Treatment Diabetic Retinopathy Study (ETDRS) charts (20/320 Snellen equivalent).

3. Clinical diagnosis of neovascular AMD with the following criteria met:
    a. Eligible for an anti-VEGF injection with macular fluid present at Day -28.
    b. At least 6 treatments of intravitreal anti-VEGF therapy in the study eye within the last year with the last 2 injections occurring at intervals not greater than 8 weeks (± 7 days).
4. A clinically meaningful reduction in excess macular fluid or macular thickness in the study eye at the discretion of the investigator between Screening Day -28 and Screening Day -14 as assessed by SD-OCT.
5. Female subjects must be:
    a. Women of non-child-bearing potential (WONCBP), or
    b. Women of child-bearing potential (WOCBP) with a negative pregnancy test at screening and must agree to use protocol defined methods of contraception for the duration of the study and refrain from breastfeeding for the duration of the study.
6. Males with female partners of child-bearing potential must agree to use protocol defined methods of contraception and agree to refrain from donating sperm for the duration of the study.
7. Willing and able to give informed consent and to comply with the study procedures and assessments.

Note: If both eyes meet the inclusion criteria, the eye with the worst VA at the screening visit will be designated as the study eye. If both eyes have the same VA, the Investigator and patient will determine the study eye.

Exclusion Criteria:

Ocular specific exclusion criteria apply to the **study eye** only.

1. Presence of other causes of choroidal neovascularization (CNV) including pathologic myopia (spherical equivalent ≥ -6 diopters), central serous chorioretinopathy, ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, and multifocal choroiditis.
2. History of vitrectomy to the study eye
3. Presence of any ophthalmologic condition that reduces the clarity of the media and that, in the opinion of the Investigator, interferes with ophthalmologic examination (e.g. advanced cataract or corneal abnormalities).
4. Intraocular surgery (including lens replacement surgery) within 3 months prior to randomization.
5. Any history of endophthalmitis.
6. Trabeculectomy or aqueous shunt or valve in the study eye.
7. Aphakia or absence of the posterior capsule. Note: previous violation of the posterior capsule is also excluded unless it occurred as a result of yttrium aluminum garnet (YAG) laser posterior

capsulotomy in association with prior posterior chamber intraocular lens implantation and at least 60 days prior to baseline.

8. Any ophthalmic condition that may require surgery or medical intervention during the study period or, in the opinion of the Investigator, could compromise visual function during the study period (e.g. severe uncontrolled glaucoma, clinically significant diabetic macular edema, ischemic optic neuropathy, retinal vasculopathies).
9. Any contraindication to IVT injection including current ocular or periocular infection.
10. Current treatment for active systemic or localized infection.
11. Participation in any systemic experimental treatment or any other systemic investigational new drug within 6 weeks or 5 half-lives of the active (whichever is longer) prior to the start of study treatment. Note: clinical trials solely involving observation, over-the-counter vitamins, supplements, or diets are not exclusionary
12. Medical or psychiatric conditions that, in the opinion of the investigator, make consistent follow-up over the 24- month treatment period unlikely, or would make the subject an unsafe study candidate.
13. Any baseline laboratory value (hematology, serum chemistry or urinalysis) that in the opinion of the Investigator is clinically significant and not suitable for study participation.
14. Known hypersensitivity to fluorescein sodium for injection or hypersensitivity to APL-2 or any of the excipients in APL-2 solution.

Sample Size:

A sample size of approximately 20 subjects with neovascular AMD will be included in this study.

Statistical Methods:

Given the exploratory nature of the study, no formal statistical hypothesis testing will be performed. Data will be presented for the cohort by study month and nominal time postdose (if appropriate).

Continuous variables will be summarized using descriptive statistics (e.g. median and mean) whilst for categorical variables the frequency and percentage in each category will be displayed.

TEAEs will be summarized by System Organ Class and Preferred Term, according to the Medical Dictionary for Regulatory Activities (MedDRA). The number of patients reporting each AE preferred term will be tabulated for all TEAEs and separately for those considered as possibly related to study treatment by the Investigator. Number of patients reporting serious adverse events (SAEs) will also be tabulated.

The number and percentage of patients achieving improvement in the secondary endpoints will be tabulated. Changes from baseline in safety endpoints will be summarized and plotted (individual and mean) over time.

PK parameters will be computed from the individual serum concentration-time data, using a non-compartmental approach. PK concentrations and parameters will be summarized and concentration profiles over time (individual and median) will be plotted.

4. SCHEDULE OF EVENTS

	Screening		Treatment													Follow-Up		Early Term. [A]
Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
Day	-28	-14	1	30	60	90	120	150	180	210	240	270	300	330	360	450	540	
Week	0	0	0	4	8	12	16	20	24	28	32	36	40	44	48	60	72	
Month	0	0	0	1	2	3	4	5	6	7	8	9	10	11	12	15	18	
Window (+ or - days)	2	3	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	
Informed Consent / Assign Screening Number	x																	
Demographic Data	x																	
Inclusion/Exclusion Criteria [B]	x	x	x															
Medical/Surgical/Ophthalmic History [C]	x																	
Blood Draw – Safety Labs [D,E]		x		x					x						x			x
Urine Sample Collection [D,F]		x		x					x						x			x
Blood Draw - PK and Anti-APL-2/ PEG Ab [D]				x					x						x			x
Vital Signs [D,G]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical Examination [H]			x													x		x
Urine Pregnancy Test [E,F]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
BCVA [I]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Slit Lamp Examination		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x

Dilated Indirect Ophthalmoscopy		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
IOP Measurement		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
SD-OCT [J]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Digital Color Fundus Photographs (DCFP) [J]			x												x			x
Fundus Fluorescein Angiograms (FFA) [J]			x												x			x
Study Eye Determination	x																	
Mandatory anti-VEGF injection	x		x															
Anti-VEGF injection (PRN)				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
APL-2 administration Injection			x	x	x	x	x	x	x	x	x	x	x	x	x			
Post-Injection Assessment [K]			x	x	x	x	x	x	x	x	x	x	x	x	x			
Concomitant Medication/ Concomitant Ocular Procedures [L]	x	x	x	x	x	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	x	x

FOOTNOTES:

A. For patients that discontinue the study early, the early termination assessments should be performed after a minimum of 30 days have passed.

B. At Day -14 (Visit 2), confirm subject eligibility through reviewing the inclusion/ exclusion criteria and receive confirmation of eligibility from the Reading Center.

C. Significant medical/ surgical history and tobacco use, including chronic and ongoing conditions. Significant ocular medical and surgical history should be obtained for the previous 1 year.

D. Obtain prior to fluorescein angiograph and before study drug administration.

E. At screening, serum pregnancy should be performed for WOCBP. If positive, subject is not eligible to continue in the study.

F. Beginning at Day 1, perform the urine pregnancy test for WOCBP at each treatment visit. If positive, perform a serum pregnancy test. If serum test is positive, study drug should not be administered and an early term visit should be completed.

G. Blood pressure, respiratory rate, heart rate, and temperature; On dosing days, vital signs should be captured pre and post dosing. Predose vitals should be captured within 90 minutes prior to dosing

H. Complete physical exam should be performed; Height and Weight should be collected at screening.

I. Perform assessments prior to dilating the eyes.

J. Images should be captured prior to dosing on dosing days. If a subject misses a study visit or images cannot be obtained at a specific visit, study staff should make every effort to obtain images at the next scheduled visit.

K. Post- injection assessments should be performed within 15 minutes after dosing by the investigator or study staff and should include a gross assessment of vision (finger-counting, hand-motion, then light perception when applicable). If subject passes gross vision test, the subject may leave the site. If subject fails gross vision test, IOP should be performed and if < 30 mmHg, the subject can be discharged. Assessments will continue every approximately 30 minutes until the subject passes gross vision test and IOP is < 30 mmHg.

L. Record concomitant medications (i.e. prescription and over the counter medications) used by the patient within 30 days of screening and throughout the subject's participation in the study. All significant concurrent ocular procedures and medications should also be recorded within the past 1 year and while on study.

5. INTRODUCTION

5.1 Background

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

5.1.1 Acute Macular Degeneration Overview

AMD is the leading cause of severe vision loss in people over the age of 65 in the United States and other Western countries.[1] In the United States, about 1.75 million people have the advanced forms of AMD.[2] The early signs of AMD (drusen and pigmentary changes) are common in individuals over age 65 and precede the advanced forms, which are visually devastating. The Centers for Disease Control and Prevention (CDC) estimates that an additional 7-8 million U.S. adults have large drusen and are therefore at risk of developing AMD. The advanced forms of AMD are classified into either macular neovascularization (neovascular, wet, or exudative AMD) or GA. Given that approximately half of the patients on anti-VEGF therapy develop retinal scars within two years of initiating treatment, it is clear that a substantial unmet need exists for advanced neovascular AMD patients alone.

Genetic susceptibility has become increasingly recognized as a risk factor and important contributor to AMD. More than 19 genetic polymorphisms have been demonstrated to influence AMD risk, with as many as 5 of these encoded by genes that modulate the complement system. Inflammatory processes, especially those mediated by complement, are thought to play a key role in AMD.[3] It is thought that these may contribute to loss of choriocapillaris, photoreceptors and RPE cells.

5.1.2 APL-2

APL-2 is formed by two pentadecapeptide (combining a cyclic tridecapeptide active C3-inhibiting moiety and a 2-amino acid linker) covalently coupled to each end of a linear 40 kDa Polyethylene Glycol (PEG) chain, so there are two peptide moieties per molecule of APL-2.

The peptide portion of the drug binds to complement C3 and is a broad inhibitor of the complement cascade, a biological process that is part of innate immunity and is involved in multiple inflammatory processes. The PEGylation of the molecule imparts slower elimination from mammalian systems following administration.

APL-2 will be supplied in clear glass vials with thermoplastic-faced stoppers and flip-off seal-caps. APL-2 is being developed for the treatment of neovascular AMD and GA.

5.2 Rationale for Treatment with APL-2

APL-2 has proven safe and tolerable in a Phase I study in patients with wet AMD (protocol POT-CP043014; NCT02461771) and in a second Phase II study in subjects with GA associated with

AMD. During the Phase II study, an imbalance in new exudation in subjects treated with APL-2 was discovered. PPD . It was noted that of the 20 APL-2-treated subjects with new study eye exudation, 14 subjects received AM treatment and 6 subjects received EOM treatment. Treatment with APL-2 was discontinued for these subjects after the onset.

Fourteen of the 21 (67%) subjects that developed new study eye exudation had a prior history of exudative AMD in the non-study fellow eye. No significant imbalance in history of exudative AMD in the fellow eye was observed among the three arms to explain the imbalance in new exudation observed in study eyes. VA data did not demonstrate clear differences between subjects developing new study eye exudation compared with those that did not.

Given these findings, further exploration is necessary to study the effects of APL-2 in subjects with neovascular AMD. In the current clinical study a complement C3 inhibitor, APL-2, will be administered to patients with neovascular AMD. The goal of the study is to assess the safety and tolerability of IVT APL-2 in neovascular AMD administered monthly. Results from this study will guide decisions to further develop APL-2 for GA and AMD.

6. NON-CLINICAL DATA

The nonclinical package was developed in accordance with ICH M3(R2) guidance and in consideration of the specific safety considerations for PEGylated products. Further details can be found in the APL-2 Investigator's Brochure.

6.1 Pharmacology

APL-2's mechanism of action and species specificity appear to be identical to those of Ac-compstatin. Both the existing in vitro complement inhibitory data and the nature of identified compstatin binding sites are consistent in predicting that only primate species would be pharmacologically relevant to study APL-2-related toxicology. All data generated in non- -primate species using compstatin and its derivative (including APL-2) indicate a lack of significant bioactivity in non-primates. The lack of C3 binding in non-primates suggests that PK data obtained in primate species (such as cynomolgus monkeys) are the most relevant, as APL-2:C3 complexes likely impact observed serum half-lives and monkey data is more representative of expected and observed PK in human subjects.

The potential for APL-2 to inhibit human ether-a-go-go gene (hERG)-encoded ion channels and pose a risk for cardiac arrhythmias indicates that such a risk is low. Similarly, no evidence of APL-2-related adverse effects on myocardial conduction, cardiovascular and respiratory systems, and body temperature control mechanisms have been observed in monkeys.

6.1.1 Pharmacokinetics

PK and toxicokinetic (TK) assessments of APL-2 have been investigated after single and repeated (9-month, 10 total dose) IVT administration to cynomolgus monkeys.

After a single IVT administration (10mg/eye in 50 µL), APL-2 was cleared from the vitreous humor of monkeys into the systemic circulation following an exponential decline with a vitreal t½ of 3.2 days. Twenty-four hours after IVT administration the mean vitreous humor APL-2 concentration was 2.1 mg/mL. Retinal APL-2 concentrations ranged from 0.709 to 4.07 µg/g of tissue at the time of terminal necropsy (Day 30). As was the case after intravenous (IV) or subcutaneous (SC) administration, intravitreally administered APL-2 was cleared from the circulatory system in an exponential fashion with a t½ of 10.4 days. The serum half-life of intravitreally administered APL-2 is somewhat longer than that observed after either SC or IV administration (t½ ≈7.5 days).

In the 9-month study in cynomolgus monkeys, serum concentrations of APL-2 were roughly dose-proportional approximately 24 hours after the first dose. Maximal serum concentrations were achieved by Test Day 6, and serum concentrations of APL-2 increased in a less-than-linear to approximately linear fashion with increasing dose. There was no evidence of bioaccumulation of APL-2 as evidenced by the fact that serum concentrations 26 days after the final dose of APL-2 were 36 to 52% lower than those achieved 26 days after the initial dose.
Intravitreal APL-2 concentrations, like serum concentrations, appeared to increase slightly between the first and second IVT dose but then stabilize between the second and third dose, supporting a conclusion of no intraocular accumulation after the first dose.

6.2 Toxicology

The potential toxicity of intravitreally administered APL-2 has been investigated in 9-month and 2-month bridging GLP (Good Laboratory Practice)-compliant studies featuring single bilateral injections in eyes of the animals every 4 weeks (10 total doses or 2 total doses, respectively). Intravitreally administered APL-2 was tolerated at all doses tested (up to and including 24.8 mg/eye). No local or systemic drug-related toxicity was observed in any animal. APL-2 was found to be minimally immunogenic in the 9-month study as evidenced by a lack of circulating antibodies in the majority of monkeys studied. A single monkey administered 12.4 mg/eye had a marginal titer of 1:20 APL-2 antibodies during Test Week 39 and a single monkey receiving 24.8 mg/eye was found to have a low 1:100 titer during Test Week 13 and a 1:500 titer during Test Week 39. No drug-related changes in CH50 values were observed at any of the drug treatment groups through Test Week 40. The NOEL for chronic (9-month) IVT dosing was concluded to be >24.8 mg/eye.

The toxicological potential of APL-2 has also been investigated in repeat-dose toxicity studies in rabbits and monkeys with other routes of administration (SC, IV) under a testing strategy designed to facilitate differentiation between potential changes attributable to APL-2 per se and those attributable to the PEG40 domain of the drug molecule. Daily subcutaneous administration of APL-2 and PEG40 for a duration of 6 months in rabbits and 9 months in monkey were associated with little systemic toxicity noted in either species beyond observations in the kidney. APL-2 and PEG40 were weakly to mildly immunogenic in rabbits, but not significantly immunogenic in monkeys. Single- or multi-tissue (or multi-organ) macrophage vacuolation was consistently observed in both species, and generally comparable in incidence and severity between APL-2- and

PEG40-treated groups; thus, it was concluded the finding were caused by the PEG40 domain present within APL-2. Renal tubular degeneration was observed with a higher incidence in the monkey 9-month study in APL-2-treated animals compared to the PEG40-treated ones, and was concluded to be APL-2-related. The no-observed-adverse-effect-level (NOAEL) for SC-administered APL-2 was <1 mg/kg/d in rabbits and approximately 7 mg/kg/d in monkeys after 6- and 9-months of chronic dosing, respectively. Similarly, no adverse effects on study parameters or endpoints were observed for APL-2 IV arms (2 doses separated by 14 days) included in 28-day repeat-dose SC studies in rabbits and monkeys.

APL-2 has not demonstrated genotoxic potential in any in vitro or in vivo genotoxicity assays conducted, nor has it shown no effect on relevant maternal and fetal endpoints in developmental toxicity and teratogenicity studies conducted in rats and rabbits.

7. CLINICAL DATA

A single Phase I single ascending dose has evaluated IV dosing of APL-2 in healthy volunteers. The safety and tolerability of APL-2 following IVT administration in humans was tested in an open label, single dose escalation, Phase I clinical study in patients with wet AMD under protocol POT-CP043014 (NCT02461771). The study was conducted in multiple ophthalmology clinical sites in the US and Australia. A single dose of APL-2 was administered on Day 1 to patients with exudative AMD currently receiving anti-VEGF standard of care. Three escalating doses of APL-2 administered IVT were studied. Three subjects received 4 mg; 3 subjects received 10 mg, and 7 subjects received 20 mg. No SAEs or drug-related adverse events (AEs) of concern were observed. It was concluded that administration of a single dose of APL-2 IVT up to 20 mg is safe and well-tolerated.

A second Phase II study is also currently ongoing (Protocol POT-CP121614; NCT02503332) to assess the safety, tolerability and evidence of activity of multiple IVT injections in subjects with GA associated with AMD. The study is being conducted at multiple ophthalmology clinical sites in the US, Australia and New Zealand. Subjects are randomized in a 2:2:1:1 manner to either receive APL-2 IVT 15 mg monthly for 12 months; Sham IVT monthly for 12 months; APL-2 IVT 15 mg EOM for 12 months; or Sham IVT EOM for 12 months. This study demonstrated statistically significant slowing of disease progression at Month 12 at the pre-specified alpha of 0.1. APL-2 administered monthly showed a 29% (p=0.008) reduction in the rate of GA lesion growth compared to sham and APL-2 administered EOM showed a 20% (p=0.067) reduction. APL-2 has been generally well tolerated. To date, the most frequently reported AEs have been related to the procedure (intravitreal injection), which are common with this type of procedure. An imbalance in new exudation in subjects treated with APL-2 and the risk of developing new exudation may be increased in subjects with a prior history of exudative AMD in the fellow eye.

Further details regarding completed studies can be found in the current APL-2 Investigator's Brochure.

7.1 Purpose of the Study

The purpose of this study is to establish the safety and tolerability of intravitreally injected APL-2 in patients with neovascular AMD.

7.2 Dose Selection

A single dose of 15 mg/100 µL, administered by IVT injection monthly, for 12 months (48 weeks), will be tested in this study (see Section 8.3).

Physician feedback injecting a 200 mg/mL solution in the ASAP 2 Phase I trial (Study POT-CP043014; NCT02461771) confirmed that 150 mg/mL is the highest practical concentration that can be routinely administered, which set the dose of the Phase II trial to 15 mg (i.e. 0.1 mL of a 150 mg/mL solution). While monthly and EOM dosing were well tolerated, the 15 mg dose given monthly was found to be the most efficacious in the Phase II trial.

7.3 Risk/Benefit

The Phase I (Study POT-CP043014; NCT02461771) and Phase II (Study POT-CP121614; NCT02503332) studies provided supporting evidence of a positive benefit-risk profile for the use of APL-2 in treating patients with AMD. Results from these studies in patients with CNV will enable to further study the safety and efficacy of APL-2 in patients with existing or new onset of CNV as monotherapy or in combination with established products. The reported safety data from these studies demonstrated an acceptable safety and tolerability profile with no clinically significant safety concerns observed. A total of 178 patients have received at least one dose (15 mg/injection) of APL-2 as part of these studies. Section 8.3 provides a summary of the study design and key results from both studies.

The safety monitoring practices employed by this protocol (complete ophthalmologic exam, IOP monitoring, OCT, vital signs, hematology, serum chemistry, urinalysis, physical exam, vital signs and AE questioning) are adequate to protect the subjects' safety. There are also risks associated with the ophthalmic procedures required for participants in this study. However, these are all standard procedures that are widely performed in ophthalmology.

In the days following any IVT injection, patients are at risk of developing endophthalmitis. If the eye should become red, sensitive to light, painful, or develop a change in vision, the patient will be instructed to seek immediate care from an ophthalmologist. Other risks of IVT injection include traumatic cataract, retinal detachment and hemorrhage. Transient increased IOP has also been identified as a risk following IVT injections.

The amount of blood (see Section 12.5) planned for collection from each subject over the 18 months of the study does not pose an undue risk in this patient population.

8. STUDY OBJECTIVES AND ENDPOINTS

8.1 Study Objectives

Objective

The objective of this study is to establish the safety of intravitreally injected APL-2 in patients with neovascular AMD.

8.2 Study Endpoints

8.2.1 Primary Endpoint

- Incidence and severity of ocular and systemic treatment- emergent adverse events (TEAEs)

8.2.2 Secondary Endpoints

- Changes from baseline in physical examination findings and laboratory parameters
- Changes from baseline in central macular thickness on OCT over 12 months

8.2.3 Pharmacokinetic Endpoint

- APL-2 pharmacokinetic concentrations

8.2.4 Exploratory Endpoint

- Number of anti-Vascular Endothelial Groth Factor (anti-VEGF) PRN injections from Visit 4 to the Exit Visit (Visit 17)

8.3 Study Design

This is an 18-Month Phase Ib/II, multi-center, open label study to assess the safety and tolerability of monthly IVT injections of APL-2 in subjects with neovascular AMD.

Patients diagnosed with AMD in the study eye, who are receiving an anti-VEGF drug and who meet all other inclusion/exclusion criteria will be included in the study. The study will include approximately 20 subjects across at least 3 U.S. sites.

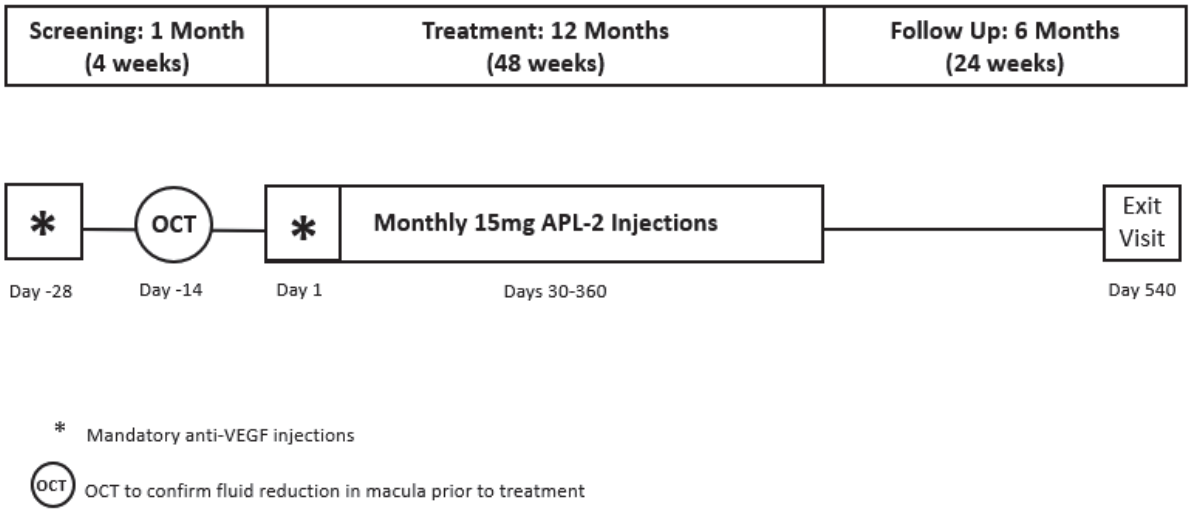
Figure 1 presents the study outline. Patients will initially be screened between Day -28 and prior to treatment on Day 1. Screening procedures will include laboratory tests, BCVA, ophthalmological exam, IOP, and SD-OCT. Upon entry into the study (after signing the informed consent), subjects will be assigned a screening number. At screening visit 1 (Day -28) subjects will have an SD-OCT taken to assess for the presence of any subretinal, intraretinal, or sub-RPE fluid, followed by an IVT dose of anti-VEGF. Subjects will return two weeks later for screening visit 2 (Day -14) and will have another OCT performed to confirm a decrease in excess fluid in the macula. Upon confirmation of less fluid in the investigator's opinion, patients who meet all inclusion and exclusion criteria will be enrolled in the study and will receive treatment with APL-2. Subjects will then return for treatment (Visit 3; Day 1). At this visit, subjects will be given a mandatory IVT dose of anti-VEGF. Treatment with anti-VEGF should be given first and IOP should be taken prior to administration of APL-2. If IOP is <21 mmHg (prior to administration of APL-2), APL-2 may be administered. If not, additional measurements should be taken until IOP reaches <21 mmHg. APL-2 should not be administered if IOP does not fall within this range.

All subjects will receive monthly APL-2 injections for 12 months (48 weeks) during their scheduled monthly treatment visits. At each treatment visit, safety assessments including vital signs, labs and urinalysis, and SD-OCT will be performed. BCVA, fundus examination, dilated indirect ophthalmoscopy and slit lamp examination will also be performed. Subjects will be assessed at each treatment visit for the need for retreatment with anti-VEGF based on pre-specific retreatment criteria. During follow-up, safety assessments will be performed for all subjects at months 15 and 18. Subjects who discontinue study treatment, can continue participation in the study and return to the clinical site for their scheduled study procedures. Subjects who fully withdraw from the study before month 12, should complete the Early Termination Visit at a minimum 30 days after their last visit.

An external, independent SMC will assess the progress and cumulative safety/tolerability data of the study.

Subjects who fail the screening procedures should not be re-screened for the study unless this is agreed in advance and documented in writing with the sponsor.

Figure 1: Study Outline



9. SUBJECT SELECTION

The study plans to enroll approximately 20 subjects with neovascular AMD in a single cohort.

9.1 Inclusion Criteria

Inclusion Criteria:

Ocular- specific inclusion criteria apply to the **study eye** only.

1. Age ≥ 60 years.

2. Normal Luminance best corrected visual acuity (NL-BCVA) of 24 letters or better using Early Treatment Diabetic Retinopathy Study (ETDRS) charts (20/320 Snellen equivalent).
3. Clinical diagnosis of neovascular AMD with the following criteria met:
    a. Eligible for an injection of an Anti-VEGF injection with macular fluid present at Day -28.
    b. Must have been treated with anti-VEGF in study eye for at least 6 months prior to joining the study.
    c. At least 6 months of intravitreal anti-VEGF therapy at intervals not greater than 8 weeks (± 7 days) for the past 2 injections in the eye that is selected to be the study eye.
4. A clinically meaningful reduction in excess macular fluid or macular thickness in the study eye at the discretion of the investigator between Screening Day -28 and Screening Day -14 as assessed by SD-OCT.
5. Female subjects must be:
    a. Women of non-child-bearing potential (WONCBP), or
    b. Women of child-bearing potential (WOCBP) with a negative pregnancy test at screening and must agree to use protocol defined methods of contraception for the duration of the study and refrain from breastfeeding for the duration of the study.
6. Males with female partners of child-bearing potential must agree to use protocol defined methods of contraception and agree to refrain from donating sperm for the duration of the study.
7. Willing and able to give informed consent and to comply with the study procedures and assessments.

Note: If both eyes meet the inclusion criteria, the eye with the worst VA at the screening visit will be designated as the study eye. If both eyes have the same VA, the Investigator and patient will determine the study eye.

Exclusion Criteria:

Ocular specific exclusion criteria apply to the **study eye** only.

1. Presence of other causes of choroidal neovascularization (CNV) including pathologic myopia (spherical equivalent ≥ -6 diopters), central serous chorioretinopathy, ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, and multifocal choroiditis.
2. History of vitrectomy to the study eye
3. Presence of any ophthalmologic condition that reduces the clarity of the media and that, in the opinion of the Investigator, interferes with ophthalmologic examination (e.g. advanced cataract or corneal abnormalities).
4. Intraocular surgery (including lens replacement surgery) within 3 months prior to randomization.

5. Any history of endophthalmitis.
6. Trabeculectomy or aqueous shunt or valve in the study eye.
7. Aphakia or absence of the posterior capsule. Note: previous violation of the posterior capsule is also excluded unless it occurred as a result of yttrium aluminum garnet (YAG) laser posterior capsulotomy in association with prior posterior chamber intraocular lens implantation and at least 60 days prior to baseline.
8. Any ophthalmic condition that may require surgery or medical intervention during the study period or, in the opinion of the Investigator, could compromise visual function during the study period (e.g. severe uncontrolled glaucoma, clinically significant diabetic macular edema, ischemic optic neuropathy, retinal vasculopathies).
9. Any contraindication to IVT injection including current ocular or periocular infection.
10. Current treatment for active systemic or localized infection.
11. Participation in any systemic experimental treatment or any other systemic investigational new drug within 6 weeks or 5 half-lives of the active (whichever is longer) prior to the start of study treatment. Note: clinical trials solely involving observation, over-the-counter vitamins, supplements, or diets are not exclusionary
12. Medical or psychiatric conditions that, in the opinion of the investigator, make consistent follow-up over the 24- month treatment period unlikely, or would make the subject an unsafe study candidate.
13. Any baseline laboratory value (hematology, serum chemistry or urinalysis) that in the opinion of the Investigator is clinically significant and not suitable for study participation.
14. Known hypersensitivity to fluorescein sodium for injection or hypersensitivity to APL-2 or any of the excipients in APL-2 solution

9.2 Approved Methods of Contraception

Approved methods of contraception include: abstinence, oral contraceptives, intrauterine device, medically acceptable barrier methods (diaphragm or condom), implantable or injectable contraceptives (like DepoProvera) 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 approved method of contraception during the study.

10. STUDY TREATMENTS

10.1 Identity of Investigational Product

APL-2 will be provided in the form of either a lyophilized or liquid formulation, in glass vials with grey stoppers and sealed with flip-off seals.

The lyophilized APL-2 or APL-2 for Injection is a sterile lyophilizate that needs to be reconstituted with 5% dextrose by investigator site staff prior to use.

The liquid APL-2 or APL-2 Intravitreal injection, 15 mg/0.1 mL (150 mg/mL) is a sterile presentation of APL-2 in an acetate buffered Trehalose solution.

Both APL-2 drug product configuration that will be injected intravitreally are sterile, clear, colorless to slightly yellowish solutions of APL-2 at approximately 150 mg/mL.

10.2 Administration of Investigational Product

10.2.1 Pre-Injection Procedure (Patient Preparation)

NOTE: It is recommended that the fellow eye is covered with a drape or 4x4 pad during the injection procedure. Study sites are to follow their standard for injection preparation and procedure. The procedures listed here are guidelines, please refer to the manual of procedures for more information.

1. Within approximately 1 hour prior to injection: Topical 1% Mydriacyl and 2.5% Phenylephrine should be applied topically to achieve adequate pupillary dilation. One drop of the topical antibiotic should also be instilled, if applicable. It is recommended that a new bottle should be used daily.
2. Apply single use topical anesthetic to the study eye as needed to achieve adequate anesthesia for the procedure. Additional local subconjunctival anesthesia (e.g., 1% lidocaine hydrochloride solution) can be used at the Site Principal Investigator's discretion.
3. Perform a local flush of povidone-iodine into the eye (enough to completely irrigate the fornices and caruncle and coat the eyelid margins). Do not scrub or manipulate the eyelids or eyelashes. Povidone- iodine bottles must not be shared between subjects.
4. A sterile drape may be used to isolate the ocular field, at the Investigator's discretion.
5. Insert a sterile eyelid speculum (solid blade, open blade, depending upon the site's standard practice). A sterile eyelid speculum must be used for all injections.
6. Place one or two drops of 5% povidone-iodine on the ocular surface at the intended injection site.

10.2.2 Dosing

Starting on Day 1 (Visit 3), subjects will receive monthly IVT doses of 15mg of APL-2 until the last dose at Month 12 (Week 48). On Day 1, anti-VEGF therapy will be administered by IVT injection, in addition to the APL-2 injection. The anti-VEGF therapy shall be administered first and the APL-2 injection shall occur not earlier than 30 minutes after anti-VEGF injection and only if the IOP is <21 mmHg

10.2.3 Investigational Product Administration

1. For the IVT injection, attach a sterile 27 gauge or 29 gauge (29 gauge for liquid formulation) Thin Wall x 1/2 inch needle. The needle should be securely threaded onto the syringe.

2. With the needle end of the syringe up, advance the plunger to the 100 µl (0.1 mL) mark to expel any air bubbles and obtain exactly 0.1 mL of liquid for IVT injection.

3. Discard the syringe and needle safely into a sharps container

4. With a permanent marker, write the subject ID number and the visit number on the label of the vial used for the injection. All used and unused vials must be kept until the site close-out visit unless other advice is given by the Sponsor, or designee.

5. Note the time of the injection in the injection worksheet/source documentation.

6. The entry site for the needle for the intravitreal injection should be 3.0 to 3.5 mm from the limbus in pseudophakic patients, and 3.5 to 4.0 mm in phakic patients. Measure the injection site with sterile calipers. The globe may be stabilized with sterile forceps if necessary.

7. Saturate a cotton-tipped applicator with sterile topical anesthetic drops and push against the globe with the swab at the planned injection site for 15-25 seconds to soften the eye. This can be repeated if necessary at the physician's discretion.

8. Absorb the excess liquid and dry the periocular skin with a 4x4 pad.

10.3 Labelling, Packaging, Storage, and Handling

10.3.1 Labelling

Labels containing study information and pack identification are applied to the investigational product(s) container.

All investigational product is labeled with a minimum of the following: protocol number, dosage form (including product name and quantity in pack), route of administration, directions for use, storage conditions, batch number and/or packaging reference, the statements “For clinical trial use only” and/or “CAUTION: New Drug – Limited by Federal (or US) Law to Investigational Use”, and name and address of sponsor.

Space is allocated on the label so that the site representative can record a unique subject identifier and date dispensed by the site to the subject.

Additional labels may, on a case-by-case basis, be applied to the investigational product in order to satisfy national, local or institutional requirements, but must not:

- Contradict the clinical study label.
- Obscure the clinical study label.
- Identify the study subject by name.

Additional labels may not be added without the sponsor’s prior full agreement.

10.3.2 Packaging

APL-2 will be supplied as either a lyophilized or liquid formulation.

APL-2 will be supplied in clear glass vials with thermoplastic-faced stoppers and flip-off seal-caps. Specific instructions for preparing APL-2 for the IVT injection procedure are provided in Section 10.2.3.

10.3.3 Storage

The lyophilized investigational product should be stored frozen at -20°C. The liquid investigational product should be stored refrigerated at 2-8°C.

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

A pharmacist or appropriately qualified designated person will be responsible for storing the investigational product appropriately . The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels as they are distributed.

Temperature monitoring is required at the investigator site (or documented storage location) to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature in monitored throughout the duration of the study and that records are maintained.

10.4 Investigational Product Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product stored, returned or destroyed at the site must be maintained.

At the conclusion of the study, any unused investigational product will either be destroyed at the investigator 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.

10.5 Re-Treatment with Anti-VEGF

In addition to receiving the study drug, APL-2, subjects will be assessed at each of the treatment visits for the need for injections of intravitreal anti-VEGF treatment. Injections may be Avastin, Lucentis, or Eyelea; however, the treatment given at baseline should be continued throughout the study (where applicable). The determination to treat with anti-VEGF should be based on the principal investigator's (PI's) discretion as to whether the subject is the same, better or worse from the previous visit. The PI should use all available assessments in making a determination for re-treating the subject with anti-VEGF.

If anti-VEGF therapy is administered on the same day as an APL-2 injection, the anti-VEGF therapy shall be administered first and the APL-2 injection shall occur not earlier than 30 minutes after anti-VEGF injection and only if the IOP is <21 mmHg.

Once the subject has completed participation (either by early termination or completing all study visits), additional treatments with anti-VEGF can be administered according to the PIs standard protocol for CNV treatment but not more frequently than recommended in the label of the selected anti-VEGF therapy.

10.6 Concomitant Medications

Any concomitant medications a participant is receiving at the start of the study, within 30 days prior to screening, or that are given for any reason during the study (except for routine medications given for ocular procedures required by the protocol, such as topical anesthetic) must be recorded in the source document and Case Report Form (CRF) including start and stop date and time, dose, route, and indication. In addition, all invasive intraocular procedures from the previous year must also be recorded in the source document including start and stop dates. Surgical anesthetics, paramedical or alternative therapies (e.g. acupuncture, massage) should also be recorded in the source documents and CRF.

Metoclopramide or other agents to prevent nausea induced by fluorescein injection may be administered at the discretion of the PI.

10.6.1 Prohibited Therapies

The PI should make a determination regarding patient continuation of therapies used to treat concomitant medical conditions. Therapies as noted in the inclusion/ exclusion criteria are prohibited as specified.

10.6.2 Endophthalmitis Treatment

All suspected cases of Endophthalmitis should be reported as a serious adverse event. The decision to treat a participant for endophthalmitis or suspected endophthalmitis will be guided by the clinical judgment of the PI. A culture sample should be performed prior to making a decision on treatment. The treatment method (pars plana vitrectomy vs. vitreous tap) and choice of antimicrobial agents are also at the discretion of the PI and should follow current standard practice patterns. The decision to use IVT steroids (e.g. dexamethasone) for the treatment of endophthalmitis is also at the discretion of the PI.

11. STUDY PROCEDURES

Please see the Schedule of Events in Section 4 for a summary of the schedule of study participation and procedures. The schedule of visit dates should be established, either 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.

Note: All ophthalmic procedures will be for both eyes throughout the study unless otherwise noted.

11.1 Screening Visit 1 (Day -28 ± 2 days)

After signing the informed consent, the subject will be screened to confirm that the subject selection criteria for the study has been met. Informed consent will be obtained at screening prior to any study related procedures being conducted.

A screen failure is a subject who has given informed consent and failed to meet the study inclusion/ exclusion criteria, and has not been randomized or administered investigational

product(s). 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.

After confirming that the subject requires an anti-VEGF injection due to the presence of any subretinal, intraretinal, or sub-RPE fluid on SD-OCT, the following assessments will be performed:

- Demographics
- Medical history (including Ophthalmic History)
- Review of inclusion/exclusion criteria
- Best corrected visual acuity using ETDRS at 4 meters (performed prior to dilating the eyes)
- Study Eye Determination
- SD-OCT
- Prior and concomitant medications
- B-HCG pregnancy test
- FSH, LH
- Adverse Events evaluation/ collection

If the subject fulfills the criteria, they will receive an anti-VEGF injection and will be asked to return to the clinic in 14 days to have further imaging (SD-OCT) taken to demonstrate if there is a response to anti-VEGF.

11.2 Screening Visit 2 (Day -14 ± 3)

Subjects that demonstrate a reduction in macular fluid (based on SD-OCT comparison from Screening Visit 1 to Visit 2) by this visit will complete the Day -14 procedures (Screening Visit 2) to ensure the rest of the study criteria are met. If all criteria are met, the subject will be scheduled to return for another anti-VEGF injection on Day 1.

- Best corrected visual acuity using ETDRS at 4 meters (performed prior to dilating the eyes)
- SD-OCT (If the investigator determines that there is a clinically meaningful reduction in macular fluid, the rest of the Day -14 procedures should be performed. If the investigator determines that they would like to wait for reading center confirmation of the images, the subject can be re-scheduled for the rest of the procedures, labs should be collected and vital signs performed at that time.)
- Urine Collection
- Urine pregnancy test (if positive, serum pregnancy test should be performed)
- Blood draw for safety labs
- Vital signs
- IOP measurement

- Dilated Ophthalmoscopy and Slip Lamp Assessment
- Evaluate and record any new concomitant medication and adverse events

11.3 Baseline Visit (Day 1 ± 8 days): Visit 3

Following successful completion of the 4-week screening period (i.e. subjects that demonstrate a reduction of macular fluid at Screening Visit 2 and meet all study criteria), subjects will enter the Treatment Period to receive another anti-VEGF injection and will receive APL-2. The following assessments outlined in the Schedule of Events (Section 4) will be performed:

Prior to treatment with APL-2:

- SD-OCT
- Urine pregnancy test (if positive, serum pregnancy test should be performed)
- Vital signs (within 90 minutes prior to dosing)
- IOP measurement (taken within 15 minutes prior to the APL-2 injection)
- Dilated Ophthalmoscopy and Slip Lamp Assessment
- Physical examination
- Evaluate and record any new concomitant medication and adverse events
- Mandatory anti-VEGF injection (Note: anti-VEGF injection is performed prior to APL-2)

APL-2 administration will occur after all of the above procedures are completed (see Section 10.2.2 for more detailed procedures). If anti-VEGF therapy is administered on the same day as an APL-2 injection, the anti-VEGF therapy shall be administered first and the APL-2 injection shall occur not earlier than 30 minutes after anti-VEGF injection and only if the IOP is <21 mmHg.

After investigational product administration:

- Vital signs
- Post Injection Assessment

11.4 Treatment Period (Day 30-360 ± 8 days): Visits 4-15

Prior to treatment:

- Best corrected visual acuity using ETDRS at 4 meters (performed prior to dilating the eyes)
- SD-OCT
- Urine pregnancy test (if positive, serum pregnancy test should be performed)
- Blood draw- safety labs (Visits 4,9 and 15)
- Blood draw- PK and anti-APL-2/ PEG (Visits 4,9, and 15)
- Vital signs (within 90 minutes prior to dosing)

- IOP measurement (taken within 15 minutes prior to the APL-2 injection)
- Dilated Ophthalmoscopy and Slip Lamp Assessment
- FA and Color Fundus Photographs (Visit 3 and Visit 15 only)
- Ophthalmic Exam
- Evaluate and record any new concomitant medication and adverse events
- Assess need for anti-VEGF injection (Note: if anti-VEGF injection is performed, should be prior to APL-2 (see Section 10.5 for more detailed procedures)

After investigational product administration:

- Vital signs
- Post Injection Assessment

11.5 Follow-up (Day 450 ± 8 days): Visit 16

All subjects that complete study treatment will be asked to return to the investigator site for follow-up visits at Month 15 and Month 18, where the assessments outlined in the Schedule of Events (Section 4) will be performed.

Subjects who discontinue treatment early and do not elect to continue their participation in the study should complete a follow-up visit 6 weeks after discontinuation of treatment and also the Exit Visit 6 weeks thereafter.

- Best corrected visual acuity using ETDRS at 4 meters (performed prior to dilating the eyes)
- SD-OCT
- Urine pregnancy test (if positive, serum pregnancy test should be performed)
- Vital Signs
- IOP Measurement
- Dilated Ophthalmoscopy and Slip Lamp Assessment
- Ophthalmic Exam
- Physical examination
- Evaluate and record any new concomitant medication and adverse events
- Assess need for anti-VEGF injection

11.5.1 Exit Visit (Day 540 ± 8 days): Visit 17

All subjects will be asked to return to the clinical facility for the Exit Visit 24 weeks after the final dose of APL-2, at Week 72.

Study participation for each subject will be concluded following completion of the Exit Visit. 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.

- Vital Signs
- Evaluate and record any new concomitant medication and adverse events
- Assess need for anti-VEGF injection

11.6 Unscheduled Follow-up Visits

All subjects will be asked to return to the clinical facility for additional follow-up visits if considered necessary by the PI.

Unscheduled follow-up visits may include (but are not limited to) any of the procedures listed in the Schedule of Events in Section 4.

11.7 Safety Monitoring Committee (SMC)

A SMC will review cumulative safety/tolerability data (e.g., physical examinations, vital signs, clinical laboratory tests, and adverse events). The SMC will have the responsibility to conduct a thorough safety assessment at regular pre-defined intervals during the treatment period of the study.

The first SMC meeting will be scheduled four months after the first subject is dosed, and at intervals of every 4 months until all subjects complete the Week 48 Visit. An *ad hoc* SMC data review may be recommended by the SMC or requested by the Sponsor at any time during the study.

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

11.8 Treatment Discontinuation and Study Withdrawal

Subject participation in this study 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's failure to comply with protocol requirements or study-related procedures.
4. Termination of the study by the Sponsor, United States Food and Drug Administration (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 study prior to study completion, the subject will undergo all procedures scheduled for study completion (Exit Visit) 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 investigator and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the PI.

If consent is withdrawn, no further study evaluations are to be performed and no attempts are to be made to collect additional data. If the subject would like to stop taking study drug but continue participation in the study, they can be scheduled for all follow-up visits and complete all of the applicable procedures except for study drug administration.

12. ASSESSMENTS

12.1 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.

12.1.1 Medical History

Medical history, including surgical or ophthalmic history (including clinically significant ocular surgeries and procedures), will be collected at Screening Visit 1.

12.1.2 Prior and Concomitant Medications

To be eligible for entry into the study subjects will be receiving anti-VEGF therapy for at least 6 months, and at a stable dose for at least 8 weeks prior to screening. All treatment with anti-VEGF during the course of the study should be recorded as a concomitant medication.

All other prior medications administered within 12 Weeks of Screening Visit 1 will be collected.

All medications and procedures administered to subjects from the time of informed consent through the End of Study Visit are regarded as concomitant and will be documented.

12.1.3 Body Height and Weight

Body height (cm) and body weight (kg) will be measured at screening visit 1 as part of the physical examination.

12.1.4 Physical Examination

All full 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.

The investigator (or designee) at the study site will examine each subject as outlined in the Schedule of Events in Section 4.

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

12.1.5 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate will be measured within 90 minutes of dosing and within approximately 30 minutes after dosing. Vital signs should be taken with the patient in a seated position after resting for 5 minutes. Vital signs will be measured before venipuncture

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, vital signs collected post-dose will be timed from the completion of the study drug administration.

12.1.6 Best-Corrected Visual Acuity (BCVA)

The best- corrected visual acuity will be measured at each visit as per the visit schedule by trained study staff. Best-corrected visual acuity testing will be assessed on ETDRS chart starting at a distance of 4m, performed by a certified VA examiner, and should precede any examination requiring administration of eye drops to dilate the eye or any examination requiring contact with the eye.

A VA Specifications procedure manual and training materials will be provided to all sites. All examiners will require certification prior to performing this assessments as part of the study.

12.1.7 Ocular Imaging

The following ocular images will be obtained and sent to the Reading Center as outlined in the visit schedule. A Reading Center manual along with training materials will be provided to all sites which will provide information on standardized procedures for the collection, storage and transmission of all images. Prior to any images being taken at the site, site personnel must be properly trained and certified and test images and systems and software must be certified and validated by the Reading Center. Only trained and certified site staff delegated the responsibility of image collection should perform this task. Ocular images obtained as part of this study are:

- Digital Color Fundus Photographs
- Fluorescein angiography
- Spectral Domain Optical coherence tomography angiography (Heidelberg Instrument)

If a patient misses a visit during which ocular images should have been taken, the images should be collected at the next scheduled study visit.

12.1.8 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Schedule of Events in Section 4. 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:

12.1.8.1 Hematology

- Hemoglobin
- Hematocrit
- Red Blood Cell count
- Platelet count
- White blood cell count with differential

12.1.8.2 Serum Chemistry

- Blood urea nitrogen (BUN)
- Creatinine
- Bilirubin (total and conjugated)
- Albumin
- Alkaline phosphatase (ALP)
- Creatine kinase
- Aspartate aminotransferase (AST)
- Alanine Aminotransferase (ALT)
- Uric acid
- Glucose
- Electrolytes (Sodium, Potassium, Chloride, Bicarbonate)

12.1.8.3 Urinalysis

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

Serum Pregnancy Test will be performed for females only. Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH) will be performed for postmenopausal females at screening Visit 1 only.

12.1.9 Post-Injection Assessment

The study eye will be assessed before and after injection to ensure that the injection procedure and/or the study medication have not endangered the health of the eye. The initial post-injection assessments should be done within 15 minutes post-injection and include a gross assessment of vision (light perception). If subject does not pass the gross vision test, IOP needs to be monitored every 30 minutes from the previous measurement until the subject passes gross vision test and IOP is < 30 mmHg. A measurement of IOP will be conducted using either Tono-pen or Goldmann applanation tonometer as outlined in the MOP. IOP must be monitored and recorded in all subjects receiving an anti-VEGF and APL-2 injection on the same day prior to and after each injection. If anti-VEGF therapy is administered on the same day as an APL-2 injection, the anti-VEGF therapy shall be administered first and the APL-2 injection shall occur not earlier than 30 minutes after anti-VEGF injection and only if the IOP is <21 mmHg.

Any subject who develops a significant and sustained raise in IOP (> 30 mmHg) or a non-adequately perfused central retinal artery (CRA) after any APL-2 injection, should be monitored according to the PI's clinical judgment and may undergo additional procedures and measurements of IOP beyond those specified in the protocol as well as IOP lowering procedures. If any concern or immediate toxicity is noted, the subject will remain at the site and will be treated according to the PI's clinical judgment.

12.2 Pharmacokinetic Assessments

12.2.1 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 Schedule of Events in Section 4. PK samples will be taken pre-dose at scheduled visits (Visits 4, 9, 15).

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

12.3 Exploratory Assessments

Blood samples will be collected via direct venipuncture at the time points delineated in the Schedule of Events in Section 4.

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

12.4 Anti- APL-2/PEG Antibody Assessments

Patients who test positive for anti-APL-2 antibodies will be followed until the antibody levels revert to baseline. Antibodies will be analyzed for titer, binding to cyclic pentadecapeptide (APL-1A-EEAcK) and PEG, and neutralizing capacity.

Patients who discontinue dosing will need to have Anti-drug Antibodies (ADA) samples collected at Follow-up visits (Month 15 and 18).

Patients who test positive for anti-APL-2 antibodies at any time will be followed with ADA samples being collected every 6 months until the antibody levels revert to baseline. Samples that test positive will be characterized by an assay that will determine antibody titer, binding to the cyclic peptide or PEG domains, and measure neutralizing capacity.

The proposed ADA sampling schedule was established to capture the ADA signal at baseline, along with any potential early onset and the dynamic profile (transient or persistent) of antibody formation while minimizing APL-2 level in the sample.

12.5 Blood Volume for Study Assessments

Table 1: Blood Volume During Study

Sample Type	Number of Visits	Approximate Volume per Visit	Approximate Volume over Course of Study

		(mL)	(mL)
Screening and Safety laboratory tests (including haematology, serum chemistry, HCG, LH, and FSH (for postmenopausal female patients only).	5	15	75
PK	4	4	16
Immunogenicity (Anti-APL-2/PEG antibodies)	4	5	20
Total Approximate Blood Volume for Study:			**111**

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

12.6 Pregnancy Tests

For WOCBP, a serum pregnancy test will be performed at screening (Visits 1 and 2) and during treatment (Visits 4, 9 and 15 if urine pregnancy test is positive). Subjects with a positive test will be excluded from the study. 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 first follow-up visit (Visit 16). Male subjects will be counseled to avoid donating sperm during the time between the first screening visit (Day -28) and the final Exit Visit.

WONCBP are not required to undergo pregnancy tests. WONCBP are defined as women meeting any of the following criteria:

- Older than 45 years with amenorrhea for > 2 years or older than 60 years with amenorrhea for > 1 year. Both confirmed by FSH and LH levels.
- Has undergone hysterectomy,
- Has undergone bilateral oophorectomy,
- Has undergone bilateral salpingectomy.

13. ADVERSE EVENTS

13.1 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 (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 electronic Case Report Form (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. AEs should be recorded beginning at screening and ending 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.

13.2 Adverse Event Assessment and Recording

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit beginning at screening and record the information in the site's source documents and on the eCRF. Questions should be asked in a manner that does not lead the subject. For each AE, the PI should note the start and resolution dates, the severity, whether it meets the definition of an SAE (see Section 13.5), the relationship of the event to the study drug, the action taken regarding study drug, and the outcome of the event. Data should be transcribed from the source documents to the CRF as per the CRF instructions.

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 Informed Consent Form (ICF) until the Exit Visit. AEs, especially those for which the relationship to test 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. Subjects will be asked how they are feeling at each Study Visit.

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.

When appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal or unknown (lost to follow-up).

13.2.1 Procedures For Recording Adverse Events

Investigators should use their best judgment to record the correct medical terminology when recording adverse events on the AE CRF. Only one AE term should be recorded in the event field on the adverse event CRF.

When recording events of infection and inflammation, the following terms and associated definitions should be used:

Irititis: the presence of inflammatory cells in the anterior chamber

Iridocyclitis: the presence of inflammatory cells in both the aqueous and vitreous

Vitritis: the presence of active inflammation in the vitreous, demonstrated by the presence of inflammatory cells (trace or greater)

Endophthalmitis: diffuse intraocular inflammation predominantly involving the vitreous cavity but also involving the anterior chamber, implying a suspected underlying infection.

A diagnosis should be recorded, whenever known, rather than individual signs and symptoms (e.g. record myocardial infarction rather than chest pain). If a diagnosis cannot be made

13.3 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. 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.

13.4 Reporting

All SAE's and pregnancies must be reported to the study Sponsor within 1 business day of discovery by sending the SAE reporting form to:

Email: PPD

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 -28 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 End of Study 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.

13.4.1 Relationship of Events to Study Treatment

All AEs that occur during this study will be recorded. The PI will review each event and assess its relationship to study drug treatment (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 following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

AE Relationship to Study Drug

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 (i.e. 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 adverse event, 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

13.4.2 Severity of Events

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

Event Severity

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.

13.5 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 one working day 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 patient or 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, which in the view of either the investigator or Sponsor places the patient or 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.

13.6 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.

13.7 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.

13.8 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 9.2) for the duration of the study.

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. 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 (see Section 13.4)

14. STATISTICS

14.1 Sample Size Justification

Given the exploratory nature of the study no formal statistical hypothesis testing will be performed and so the sample sizes of both parts of the study are not based upon statistical power of the study. When no untoward adverse events occurred, we can, with a 95% confidence, rule out the event rate of >25.9% for a sample size of n = 10 subjects, or >13.9% for n = 20 subjects.

Twenty neovascular AMD patients will be enrolled into a single cohort.

14.2 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 in the SAP. 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 SAP or from what is outlined in the protocol will be discussed in the final study report.

All endpoints will be summarized by treatment group and visit. Continuous data will be summarized using descriptive statistics (e.g. mean and standard deviation) and categorical data will be summarized using frequency tables (counts and percentages).

14.2.1 Analysis Populations

14.2.1.1 Screened Population

The screened/run-in analysis set will include all patients who signed the informed consent form, are screened for participation, and were given initial anti-VEGF therapy in this study. This set will be used only for the purpose of describing patient disposition.

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

The safety analysis set will include all patients who receive a dose of APL-2.

14.2.1.3 Pharmacokinetic (PK) Population

The PK population will include all subjects in the ITT population who receive APL-2 and have at least 1 evaluable post-dose PK measurement.

14.2.1.4 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 make decisions on how to deal with any data issues (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.

14.2.2 Analyses

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

14.2.2.1 Primary Endpoint

The primary endpoint is the incidence and severity of ocular and systemic Treatment- Emergent Adverse Events (TEAEs).

14.2.2.2 Secondary Endpoints

Secondary endpoints for the study are:

- Changes from baseline in physical examination findings and laboratory parameters
- Changes from baseline in central macular thickness on OCT over 12 months

14.2.2.3 Pharmacokinetic Endpoints

- APL-2 pharmacokinetic concentrations.

14.2.2.4 Exploratory Endpoints

- Number of anti-VEGF (PRN) injections from Visit 4 to the Exit Visit (Visit 17)

14.2.3 Safety Analyses

All safety endpoints will be evaluated and safety summaries will be presented over the screening/run-in period, 48 weeks of treatment and 24 weeks of follow-up, as well as the overall duration of the study.

14.2.3.1 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.

Treatment-emergent adverse events will be summarized by System Organ Class and Preferred Term, in accordance with the MedDRA coding dictionary. The number of subjects reporting each AE preferred term will be tabulated for all TEAEs and separately for those considered as possibly related to study treatment by the Investigator. Number of subjects reporting SAEs will also be tabulated.

14.2.3.2 Clinical Laboratory Tests

Changes from baseline in laboratory will be summarized using descriptive statistics by treatment, visit and nominal time post dose. Baseline will be taken as the last measurement prior to the first dose of APL-2.

Out of range values will be flagged in the data listings.

14.2.3.3 Vital Signs

Changes from baseline in vital signs will be summarized using descriptive statistics by treatment, visit and nominal time post dose. Baseline will be taken as the last measurement prior to the first dose of APL-2.

14.2.4 Pharmacokinetic Analyses

The PK concentrations will be evaluated using the PK Population.

Concentrations will be summarized using descriptive statistics over time in the treatment period.

Individual subject concentration-time data will be plotted against actual sampling time. Median profiles of the concentration-time data, using nominal sampling times, will also be presented. Both linear-linear and linear-log plots will be presented.

Population pharmacokinetic and exposure-response modelling of the safety and exploratory data will be described in an APL-2 Population Pharmacokinetic/Pharmacodynamic Analysis Plan. The methods will be based on the FDA Guidances for both Exposure-Response and Population Pharmacokinetics (FDA Guidance for Industry Population Pharmacokinetics, FDA Guidance for Exposure-Response Relationships).

14.2.5 Other Data Analyses (Treatment Group Comparability)

Pharmacodynamic analyses and other exploratory analyses will be further defined in the study SAP. Demographic data, baseline characteristics, physical examination, concomitant medication, medical history data and study medication exposure will be summarized by treatment group.

World Health Organization (WHO) and MedDRA coding dictionaries will be used for the concomitant medications and medical histories respectively.

14.3 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 study-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.

14.4 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) national 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.

14.4.1 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.

14.5 Ethics

14.5.1 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, applicable regulations, the ethical principles set forth in the Declaration of Helsinki, and the ICH Harmonized Tripartite Guidance for Good Clinical Practice, E6, R2 (ICH GCP).

14.5.2 Institutional Review Board/Ethic Committee

The study protocol, any Versions 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 the principles and requirements described in ICH Guidance E6 and national and local regulations as deemed appropriate.

14.5.3 Subject Information and Consent

It is the responsibility of the investigator or designee to obtain written informed consent from all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (i.e., a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time and site personnel should properly document the informed consent process followed.

A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor or designee prior to the start of the study. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

If there are any changes/Versions 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.

14.5.4 Confidentiality

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

14.5.5 ClinicalTrials.gov

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

14.5.6 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.

14.6 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.

14.7 Protocol Versions

Any Versions to the study protocol deemed necessary as the study progresses will be discussed between Sponsor and the PI. The PI will not implement any changes to the protocol without an agreement by the Sponsor and prior review and documented approval from the IRB/IEC of an Version, except where necessary to eliminate immediate hazards to study subject or when the changes involve only logistical or administrative aspects of the study (*e.g.*, change in staff, telephone numbers).

Changes resulting in Versions will be made jointly between the Sponsor and the PI and must be confirmed in writing. Version(s) will be approved and signed off in the same way as the protocol.

14.8 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).

14.9 Finance and Insurance

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

14.9.1 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.

Apellis will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Apellis adheres to external guidelines (e.g. Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Apellis. The purpose of

the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Apellis products or projects must undergo appropriate technical and intellectual property review, with Apellis agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Apellis, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

15. REFERENCES

1. Rein DB, Wittenborn JS, Zhang X, et al. Forecasting age-related macular degeneration through the year 2050: the potential impact of new treatments. *Archives of ophthalmology.* 2009;127(4):533-540.
2. Friedman DS, O'Colmain BJ, Munoz B, et al. Prevalence of age-related macular degeneration in the United States. *Archives of ophthalmology.* 2004;122(4):564-572.
3. Sunness JS, Bressler NM, Tian Y, Alexander J, Applegate CA. Measuring geographic atrophy in advanced age-related macular degeneration. *Investigative ophthalmology & visual science.* 1999;40(8):1761-1769.