Apellis

Protocol No.: POT-CP121614

A Phase II, Multicenter, Randomized, Single-Masked, Sham-Controlled Study of Safety, Tolerability and Evidence of Activity of Intravitreal APL-2 Therapy in Patients with Geographic Atrophy (GA) - FILLY -

FILLY

Phase:	II
Version:	3.0
Date:	1 May 2017

INVESTIGATOR AGREEMENT

Long Title:	A Phase II, Multicenter, Randomized, Single-Masked, Sham-Controlled Study of Safety, Tolerability and Evidence of Activity of Intravitreal APL-2 Therapy in Patients with Geographic Atrophy (GA)
Short Title:	FILLY
Protocol Number, Version and Date	POT-CP121614 / Version 3.0 / 1 May 2017
Study Phase:	Phase II
Sponsor Name and Address:	Apellis Pharmaceuticals 6400 Westwind Way, Suite A Crestwood, KY 40014
Investigational Test Article:	APL-2 Injection
US IND#:	124784
Indication Studied:	Geographic Atrophy associated with Age-Related Macular Degeneration
Investigator Agreement:	I have read the clinical study 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)

1. SYNOPSIS

Study Title

A Phase II, Multicenter, Randomized, Single-Masked, Sham-Controlled Study of Safety, Tolerability and Evidence of Activity of Intravitreal APL-2 Therapy in Patients with Geographic Atrophy (GA) – FILLY -

Protocol Number, Version and Date

POT-CP121614 / Version 3.0 / 1 May 2017

Investigtional Product, Dose and Route of Admistration

- APL-2
- 15 mg/100 µL
- Intravitreal (IVT) Injection

Study Arms

Arm		Randomization
APL-2 15 mg/100 µL Monthly for 12 months	AM	2
APL-2 15 mg/100 µL EOM for 12 months	AEOM	2
Sham Monthly for 12 months	SM	1
Sham EOM for 12 months	SEOM	1

EOM = Every-Other-Month

Study Phase and Type

Phase II, Multicenter, Randomized, Single-Masked, Sham-Controlled.

Study Objectives

The primary objectives of the study are to assess the safety, tolerability and evidence of activity of multiple intravitreal (IVT) injections of APL-2 in subjects with Geographic Atrophy associated with Age-Related Macular Degeneration (AMD)

Number of Subjects and Sites

- 240 subjects (200 evaluable)
- 40 multinational sites.

Inclusion Criteria

Unless specified otherwise, ocular specific inclusion criteria apply to the **study eye** only.

1. Male or Female.
2. Age ≥ 50 years.
3. Best corrected visual acuity (BCVA) of 24 letters or better using Early Treatment Diabetic Retinopathy Study (ETDRS) charts (20/320 Snellen equivalent).
4. Diagnosis of GA of the macula secondary to AMD, confirmed within 14 days prior to randomization by the central reading

center (CRC) using Fundus Autofluorescence (FAF) images, as well as the following criteria:

a. Total GA area must be ≥ 2.5 and ≤ 17.5 mm^2 (1 and 7 disk areas [DA] respectively), determined by screening images of FAF.

b. If GA is multifocal, at least one focal lesion must be ≥ 1.25 mm^2 (0.5 DA).

c. GA can be completely visualized on the macula centered image.

d. GA must be able to be photographed in its entirety.

e. GA must be able to be measured separately from any areas of peripapillary atrophy as assessed by the CRC.

f. Presence of any pattern of hyperautofluorescence in the junctional zone of GA. Absence of hyperautofluorescence (i.e. pattern = none) is exclusionary. See Holz et al. 2007.[1]

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.

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.

Note: If both eyes meet the inclusion criteria, the eye with the worst visual acuity at the screening visit will be designated as the study eye. If both eyes have the same visual acuity, the right eye will be used as the study eye.

Exclusion Criteria

Unless specified otherwise, ocular specific exclusion criteria apply to the **study eye** only.

1. GA due to causes other than AMD such as Stargardt disease, cone rod dystrophy or toxic maculopathies like plaquenil maculopathy.

2. Spherical equivalent of the refractive error demonstrating > 6 diopters of myopia or an axial length >26 mm.

3. Any history or current evidence of exudative ("wet") AMD including any evidence of retinal pigment epithelium rips or evidence of neovascularization anywhere in the retina based on fluorescein angiogram as assessed by the CRC.
4. Retinal disease other than AMD; however, benign conditions of the vitreous or peripheral retina are not exclusionary (i.e. pavingstone degeneration).
5. 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).
6. Any ophthalmologic condition that prevents adequate imaging of the retina judged by the site or CRC.
7. Intraocular surgery (including lens replacement surgery) within 3 months prior to randomization.
8. Aphakia or absence of the posterior capsule.

   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 Day 0.
9. Any ophthalmic condition that may require surgery during the study period.
10. Any contraindication to IVT injection including current ocular or periocular infection.
11. History of uveitis or endophthalmitis.
12. History of IVT injection at any time.
13. Participation in another interventional clinical study, or use of any experimental treatment for AMD or any other 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.
14. Medical or psychiatric conditions that, in the opinion of the investigator, make consistent follow-up over the treatment period unlikely, or in general a poor medical risk because of other systemic diseases or active uncontrolled infections.

15. Any screening laboratory value (hematology, serum chemistry or urinalysis) that in the opinion of the Investigator is clinically significant and not suitable for study participation.
16. Hypersensitivity to fluorescein.

Endpoints

The primary endpoints are to demonstrate superiority of monthly and every-other-month (EOM) APL-2 IVT injections compared to sham injections based upon the mean change in GA lesion size as measured by FAF and the number and severity of treatment emergent adverse events (TEAEs).

Primary Efficacy Endpoint

- The primary endpoint is the change in square root geographic atrophy (GA) lesion size from baseline to Month 12 as measured by FAF.

Primary Safety Endpoint

- Number and severity of local and systemic treatment emergent averse events (TEAE).

Secondary Endpoints

- Secondary Efficacy Endpoints

- Mean change in GA lesion size as measured by SD-OCT.
- Change in best-corrected visual acuity (BCVA).
- Change in low luminance best-corrected visual acuity (LL-BCVA).
- Relationship between GA lesion size changes and changes in BCVA.
- Relationship between LL-BCVA and low luminance deficit with GA lesion size changes.
- Changes in distance of GA lesion from fovea (foveal encroachment).
- Change in drusen size over time.
- Relationship between GA lesion size changes and presence of reticular pseudodrusen.
- Relationship between genetic polymorphisms associated with AMD with GA progression and response to APL-2.
- Comparison of incidences of new onset macular neovascularization (MNV) between the treatment and sham arms.

- Secondary Safety Endpoints

- Changes in vital signs.

- Increase in intraocular pressure (IOP).
- Infectious endophthalmitis (defined as treatment for infectious endophthalmitis) or non-infectious endophthalmitis.
- Ocular inflammation.
- Retinal detachment or tear.
- Vitreous hemorrhage.
- Any ocular surgical intervention (incisional or non-incisional).

- Pharmacokinetic (PK) parameters

- Exposure after multiple APL-2 IVT injections (AUC).
- Serum maximum observed concentration (C_{max}).
- Time to maximum measured concentration (T_{max}).
- Terminal elimination half-life ($t_{1/2}$).

Study Design

This is a Phase II, prospective, multicenter, randomized, single-masked, sham-controlled study to assess the safety, tolerability and evidence of activity of multiple IVT injections of APL-2 in subjects with GA associated with Age-Related Macular Degeneration.

Patients diagnosed with GA associated with age-related macular degeneration in the study eye and who meet all inclusion/exclusion criteria will be included in the study. The study will randomize approximately 240 subjects to obtain at least 200 evaluable subjects across 40 multinational sites.

Subjects should be screened within 14 days before receiving APL-2. Upon entry into the study, subjects will be assigned a screening number. Patients who meet all inclusion and exclusion criteria and are confirmed as eligible by the CRC will return to the clinic for randomization and treatment on Visit 2 (Day 0). At this visit, subjects will be randomized in a 2:2:1:1 manner to receive APL-2 Monthly (AM), APL-2 Every-Other-Month (AEOM), Sham injection Monthly (SM) or Sham injection Every-Other-Month (SEOM), respectively.

All subjects will return to the clinical site on Day 7 to assess acute safety after the first injection. After that, subjects in the monthly groups will return to the clinical site for additional APL-2 (or Sham) injections and study procedures every month until Month 12. Subjects in the EOM groups will return to the clinical site for additional APL-2 (or Sham) injections and study procedures every two months until Month 12.

All subjects will return for follow-up visits on Months 15 and 18 (3 and 6 months after Month 12, respectively).

Subjects who discontinue study treatment, can continue participation in the study and return to the clinical site for their scheduled study procedures (with the exception of APL-2/Sham administration).

Subjects who fully withdraw from the study before Month 12, should complete the Termination Visit.

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2. STUDY FLOW CHARTS

Monthly Groups Visit Schedule

	Screening	Treatment														FU	Termin.
Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Day	-14	0	7	30	60	90	120	150	180	210	240	270	300	330	360	450	540
Deviation Allowed (+ or - days)	5	0	2	6	6	6	6	6	6	6	6	6	6	6	6	14	14
Month	-0.5	0	0	1	2	3	4	5	6	7	8	9	10	11	12	15	18
Informed Consent / Assign Screening Number	x																
Demographic Data	x																
Inclusion/Exclusion Criteria [A]	x	x															
Medical/Ocular History	x																
Blood Draw – Safety Labs [B]	x				x				x						x		x
Urine Sample Collection	x				x				x						x		x
Blood Draw - PK and Anti-APL-2 Ab	x		x	x	x	x	x	x	x	x	x	x	x	X	x	x	x
Blood Draw – Genotyping (if applicable) [C]					x												
Vital Signs [D]	x	x	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x
Urine Pregnancy Test [E]				x	x	x	x	x	x	x	x	x	x	X	x	x	x
BCVA	x	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	x	SE	x
LL-BCVA	x	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	x	SE	x
IOP Measurement	x	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	x
Slit Lamp Examination	x	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	x
LOCS III Lens Grading [F]	x	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	x
Dilated Binocular Indirect Ophthalmoscopy	x	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	x
SD-OCT [G]	x				SE				SE						SE		x
Fundus Autofluorescence Photographs (FAF) [G]	x				x				x						x		x
Infrared Reflectance (IR) [G]	x				x				x						x		x
Digital Color Fundus Photographs (DCFP)	x																x
Fundus Fluorescein Angiograms (FFA)	x																x
Study Eye Determination	x																
Randomization		x															
APL-2 administration or Sham Injection		x		x	x	x	x	x	x	x	x	x	x	x	x		
Post-Injection Assessment [H]		x		x	x	x	x	x	x	x	x	x	x	x	x		
Concomitant Medication / Adverse Events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

SE= Study eye only
See notes below EOM visit schedule table.

Every-Other-Month (EOM) Groups Visit Schedule											
	Screening	**Treatment**								**FU**	**Termin**
Visit #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Day	**-14**	**0**	**7**	**60**	**120**	**180**	**240**	**300**	**360**	**450**	**540**
Deviation Allowed (+ or - days)	5	0	1	6	6	6	6	6	6	14	14
Month	**-0.5**	**0**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**15**	**18**
Informed Consent / Assign Screening Number	x										
Demographic Data	x										
Inclusion/Exclusion Criteria [A]	x	x									
Medical/Ocular history	x										
Blood Draw – Safety Labs [B]	x			x		x			x		x
Urine Sample Collection	x			x		x			x		x
Blood Draw - PK and Anti-APL-2 Ab	x		x	x	x	x	x	x	x	x	x
Blood Draw – Genotyping (if applicable) [C]				x							
Vital Signs [D]	x	x	x	x	x	x	x	x	x	x	x
Urine Pregnancy Test [E]				x	x	x	x	x	x	x	x
BCVA	x	SE	SE	SE	SE	SE	SE	SE	x	SE	x
LL-BCVA	x	SE	SE	SE	SE	SE	SE	SE	x	SE	x
IOP Measurement	x	SE	SE	SE	SE	SE	SE	SE	SE	SE	x
Slit Lamp Examination	x	SE	SE	SE	SE	SE	SE	SE	SE	SE	x
LOCS III Lens Grading [F]	x	SE	SE	SE	SE	SE	SE	SE	SE	SE	x
Dilated Binocular Indirect Ophthalmoscopy	x	SE	SE	SE	SE	SE	SE	SE	SE	SE	x
SD-OCT [G]	x			SE		SE			SE		x
Fundus Autofluorescence Photographs (FAF) [G]	x			x		x			x		x
Infrared Reflectance (IR) [G]	x			x		x			x		x
Digital Color Fundus Photographs (DCFP)	x										x
Fundus Fluorescein Angiograms (FFA)	x										x
Study Eye Determination	x										
Randomization		x									
APL-2 administration or Sham injection		x		x	x	x	x	x	x		
Post-Injection Assessment [H]		x		x	x	x	x	x	x		
Concomitant Medication / Adverse Events		x	x	x	x	x	x	x	x	x	x

SE= Study eye only

A. On visit 2, review inclusion/exclusion and confirm eligibility by the Central Reading Center (CRC).
B. Includes HCG for WOCBP and FSH/LH blood for postmenopausal females at screening.
C. Genotyping will only be performed at selected sites.
D. On injection visits, vital signs will be measured within approximately 1 hour prior to dosing and within 30 minutes after dosing.
E. Only WOCBP
F. If a lens finding is noted during the slit-lamp examination, at any visit, then the finding should be further characterized with LOCS III. All subsequent visits for that patient should include LOCS III.
G. On injection visits, SD-OCT, FAF and IR should be performed before APL-2 (or Sham) administration. IR will only be done at selected clinical sites with Heidelberg Spectralis® system.
H. Initial assessment must be done within 15 minutes after dosing. Additional assessments should be done every approximately 30 minutes, if needed.

3. ABBREVIATIONS

Abbreviation	Term
AE	*Adverse Event*
AEOM	*APL-2 Every-Other-Month*
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*
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*
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*
EOM	*Every Other Month*
ERG	*Electroretinography*

Abbreviation	Term
ETDRS	*Early Treatment Diabetic Retinopathy Study*
FAF	*Fundus Autofluorescence*
FFA/FA	*Fundus Fluorescein Angiography or Fluorescein Angiography*
FSH	*Follicle-Stimulating Hormone*
G	*Gauge*
GA	*Geographic Atrophy*
GCP	*Good Clinical Practice*
HCG	*Human Chorionic Gonadotropin*
HIPAA	*Health Insurance Portability and Accountability Act*
ICF	*Informed Consent*
ICH	*International Conference on Harmonization*
IEC	*Independent Ethics Committee*
IOP	*Intra Ocular Pressure*
IR	*Infrared Reflectance*
IRB	*Institutional Review Board*
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*
LOCS III	*Lens Opacities Classification Systems III*
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 Adverse Effect Level*
OCT	*Optical Coherence Tomography*
PDT	*Photodynamic Therapy*
PEG	*Polyethylene Glycol*
PEG40	*Polyethylene Glycol (40 kDa nominal molecular weight)*

Abbreviation	Term
PI	*Principal Investigator. (PI and Investigator are used interchangeably)*
PK	*Pharmacokinetics*
PP	*Per Protocol*
QC	*Quality Control*
RBC	*Red Blood Cell*
RPE	*Retinal Pigment Epithelium*
SAE	*Serious Adverse Event*
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*
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*

4. INTRODUCTION

4.1 Background

This study is being conducted as part of a series of studies for the clinical development of APL-2 for advanced Age-related Macular Degeneration (AMD) (neovascular AMD and geographic atrophy [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 GA associated with AMD.

4.1.1 Age-Related Macular Degeneration

Age-related macular degeneration is the leading cause of severe vision loss in people over the age of 65 in the United States and other Western countries.[2] In the United States, about 1.75 million people have the advanced forms of AMD.[3] 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 advanced forms of AMD are classified into either macular neovascularization (neovascular, wet, or exudative AMD) or GA.

Exudative AMD is characterized by the abnormal growth of choroidal vessels into the subretinal space. The subsequent exudation of fluid, lipid and blood causes retinal edema resulting in vision loss and symptoms of metamorphopsia. The growth of these new vessels is accompanied by the proliferation of fibrous tissue; the continued growth of these fibroblastic lesions into the macula results in progressive, severe and irreversible vision loss.[4,5] Although exudative AMD is only present in about 10% of all AMD cases, the majority (90%) of the severe rapid visual loss due to advanced AMD is attributable to the development of macular neovascularization (MNV). Without treatment, most affected eyes will develop poor central vision (20/200) within 12 months. Anti-VEGF agents, such as ranibizumab (Lucentis®), aflibercept (Eylea®) and off-label bevacizumab (Avastin®), are the current standard-of-care for the treatment of exudative AMD.

Geographic Atrophy is a disease characterized by thinning and loss of the retinal pigment epithelium (RPE) and concurrent atrophy of photoreceptors and choriocapillaris.[6,7,8] Clinically, GA is characterized by islands of dead retinal cells in the back of the eye that gradually expand. Although GA can result in significant visual function deficits in reading, night vision, and dark adaptation, and produce dense, irreversible scotomas in the visual field, the initial decline in VA may be relatively limited if the fovea is spared. When the fovea is involved, GA quickly causes blindness. GA is responsible for approximately 20% of all legal cases of blindness in North America with increasing incidence and prevalence owing to a higher life expectancy.[6] While there is treatment for exudative AMD with anti-VEGF therapies, no therapy exists for GA which is usually bilateral and relentlessly progressive.

4.1.2 APL-2

APL-2 (PEGylated peptide) is composed of two small cyclic peptides covalently coupled via a linker to each end of a linear 40kDa polyethylene glycol (PEG40) chain. The peptide portion of the drug (a.k.a. POT-4/AL-78898A/APL-1) is a small 13-amino acid cyclic peptide with 12 natural amino acids and a single synthetic amino acid (methyltryptophan). APL-1 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 for Injection (drug product) is provided as vials of lyophilized APL-2 to be reconstituted in 5% dextrose prior to administration. APL-2 is being developed for the treatment of neovascular AMD and geographic atrophy.

4.1.3 Nonclinical Data

This section is intended to briefly summarize the information on the safety of IVT injections of APL-2. For complete and detailed information refer to the Investigator's Brochure.

The safety and tolerability of APL-2 following IVT administration was determined by a number of non-clinical studies, including a pivotal repeated-dose 9-month chronic study in cynomolgus monkeys performed by Charles River Laboratories (CRL). In this study, male and female monkeys received IVT doses of APL-2 of 0 (vehicle control), 3.1, 12.4, or 24.8 mg/eye in volumes of either 50 or 100 µL/eye. A fifth group of monkeys received 22.4 mg/eye of PEG40 on the same schedule. Injections were performed every 4 weeks for 38 weeks. This study examined PK parameters in addition to the local and systemic toxicology of APL-2 after monthly IVT injections. The accumulated data from this study (10 injections) supports the multiple dose clinical testing proposed in this protocol. It was concluded that administration of APL-2 via IVT injections (doses up to 24.8 mg/eye) was well tolerated showing no sign of any local or systemic drug-related changes after 10 injections at a frequency of once every 4 weeks.

Additional non-clinical studies in monkeys and rabbits, including toxicological studies testing other routes of administration such as subcutaneous (SC) and intravenous (IV), have further defined APL-2's safety profile. APL-2 has been shown to be well tolerated through all three routes of administration (IVT, SC, and IV) and have no significant adverse effects during safety pharmacology studies (*in vivo* cardiopulmonary telemetry and *in vitro* hERG inhibition assay) and genotoxicity studies (AMES, *in vitro* aneugenicity and clastogenicity in TK6 cells, and *in vivo* clastogenicity in mouse micronuclei). Some mild immunogenicity was observed after SC administration in rabbits but not in monkeys.

4.1.3.1 Pharmacokinetics

Pharmacokinetic parameters after IVT injections have been assessed in cynomolgus monkeys receiving a single injection of 10 mg of APL-2 in each eye. Vitreous humor APL-2 concentrations ranged from 706 to 3060 µg/mL on Day 2 (first sampling time point). There was an exponential decline in APL-2 concentrations over time and IVT concentrations ranging from below-quantification-level (BQL) to 11.6 µg/mL were reported on Day 28. From these data, an IVT half-life ($t_{½}$) of approximately 3.2 days was calculated. Serum concentrations peaked between Days 7 and 10, and ranged from 13.4 to 62.0 µg/mL at their maximum. There was an exponential decline in APL-2 concentrations afterwards and concentration ranging from 2.43 to 17.3 µg/mL where measured on Day 28. The apparent APL-2 serum half-life ($t_{½}$) after IVT injection was 10.4 days.

Intravitreal injections every 4 weeks in monkeys do not seem to cause significant drug accumulation in vitreous humor or serum based on available PK data from the 9-month ocular study. Mean intravitreal APL-2 concentrations increased slightly between the first and second IVT doses then stabilized between the second and third doses, suggesting little potential for intraocular accumulation of the drug. Serum concentrations of APL-2 peaked 6 days after each IVT injection then exhibited exponential declines with minimal concentrations being measured 28-days post-dose (immediately prior to the next IVT dose). Mean minimal serum APL-2 concentrations (26 to 28 days after IVT injection) were 15 to 30% of the corresponding maximal concentration.

Mean maximal serum concentrations of APL-2 after the tenth IVT dose were significantly lower (27 to 57%) than those achieved after the initial dose. Similarly, mean minimal serum concentrations of APL-2 (26-days after the tenth injection) were roughly 50% lower than those determined 28-days after the initial dose.

4.1.3.2 Toxicology

Local toxicity

A 9-month (39 weeks) chronic repeat-dose toxicology study was done to determine the potential toxicity, antigenicity, and toxicokinetic profile of APL-2 when administered to cynomolgus monkeys by IVT injection every 4 weeks for 36 consecutive weeks at doses of 3.1, 12.4, and 24.8 mg/eye.

All animals survived through to Test Week 39. There were no test article effects on clinical observations, body weights, food consumption, hematology, clinical chemistry, CH50, macroscopic pathology or organ weights. APL-2 was minimally antigenic as evidenced by one mid-dose monkey had a marginal titer of 1:20 to APL-2 during week 39 and one monkey the high dose group was found to have low titer 1:100 antibodies to APL-2 during week 13 and 1:500 titer during week 39. There were no test article effects on any ophthalmological parameters monitored, which included indirect and slit lamp, spectral domain optical coherence tomography (SD-OCT), electroretinography (ERG), and tonometry.

Two APL-2 mid-dose animals and one APL-2 high-dose animal exhibited marked inflammation post IVT injection in one eye after the first and third injection, respectively. The inflammation gradually diminished in subsequent weeks upon proper treatment with anti-inflammatory drugs and/or antibiotics. These changes are consistent with incidental inflammation associated with IVT injection procedures and were concluded not to be drug-related.

The ERG responses were normal for both eyes of all animals at baseline, and remained within normal limits through Week 39. No drug-related changes in IOP were observed in any group through Week 39. Spectral domain optical coherence tomographic examinations revealed no APL-2 associated retinal changes. Decreases in macular volume, ≥1.5 but ≤3 and >3 mm^3, were observed in one vehicle control and one high-dose monkey, respectively. Decreased retinal thickness was observed in vehicle control and PEG40 monkeys but not in APL-2 dosed animals. A single mid-dose animal exhibited an increase in central retinal thickness of >40 µm

in the left eye and an increased central retinal thickness ≥20 but ≤40 µm in the right eye. These changes were not considered APL-2-related.

Histopathological examinations of both eyes from every animal on study revealed no evidence of APL-2 mediated changes. Eyes of both vehicle control and drug treated monkeys were observed to have fibrosis/pigmented macrophages in the vitreous or needle tracks. The incidence and severity of these changes were identical in all groups regardless of agent injected. Histopathological examination of approximately 50 additional tissue/organs from study animals revealed no evidence of APL-2 attributable changes.

The results of this 9-month chronic study in cynomolgus monkeys support the safety of chronic IVT injections of APL-2 at a 4-week interval in man.

Additional toxicology information

APL-2 had no significant effect on hERG action potential *in vitro*. In addition, APL-2 had no effect during *in vivo* assessments of cardiovascular and respiratory parameters or body temperature when administered SC to telemeterized monkeys.

Apellis has assessed APL-2 in repeat-dose subcutaneous (SC) and intravenous (IV) toxicity studies in rabbits and monkeys. In one of these studies a PEG40 group was included to facilitate identification of changes that are likely attributable to the PEG portion of APL-2 as compared to those elicited by either the peptide moiety or the APL-2 molecule *per se*.

The results of studies during which rabbits and monkeys received SC daily doses of APL-2 (0.25, 1. 3, 7, 28, or 140 mg/kg/d) for up to 28-days or 2 intravenous (IV) doses of APL-2 (42 mg/kg) 14 days apart affords support for the projected systemic safety of APL-2 administered by the IVT route in the proposed clinical trials. After 28 days of SC administration or 2 IV doses, there were neither grossly observable nor clinical pathology changes in either species. A primary microscopic change observed at SC doses of 3 mg/kg/d and higher, common to both APL-2 and PEG40 in both species, was multi-tissue macrophage vacuolation.

Administration of other clinically used PEGylated compounds to laboratory species has been associated with macrophage vacuolation which is believed to be a naturally-occurring adaptive change secondary to the clearance of large molecules from the tissues. Although frequently observed, macrophage vacuolation has not been associated with either behavioral or clinical effects in animals nor with adverse events in humans. The repeated SC dose “no observable effect dose” for macrophage vacuolation in both rabbits and monkeys was determined to be approximately 3 mg/kg/d which was associated with a mean maximal serum concentration in monkeys of approximately 500 µg/mL after 28 days of consecutive SC dosing. That no observable effect serum concentration in SC dosed monkeys is approximately 3-fold higher than the maximal serum concentration achieved in monkeys after the initial IVT administration of 24.8 mg/eye and 6 times higher than that achieved after the tenth IVT injection.

Renal tubular degeneration was also observed in some monkeys administered 28 or 140 mg/kg/d of APL-2 by the SC route. Target organ toxicity in the kidney has also been associated with administration of PEG *per* se to animals. Renal tubular degeneration was also observed in monkeys administered PEG40 and this change was comparable to that observed in the high-

dose APL-2 groups; thus, the peptide did not exacerbate findings attributable to PEG40. The daily SC doses associated with renal tubular degeneration in monkeys, 28 and 140 mg/kg/day, result in maximal serum APL-2 concentrations that are 11 and 24 fold, respectively higher than those associated with IVT administration of 24.8 mg/eye.

The remaining toxicological findings in both the rabbit and the monkey, including clinical pathology changes and/or inflammatory reactions at the injection sites, are monitorable in the clinic. In rabbits, SC administration of APL-2 was slightly to mildly immunogenic; however, SC APL-2 was not associated with any observed immunologic effects in monkeys.

APL-2 and PEG40 did not induce genotoxicity under conditions tested. Both agents were negative in a bacterial reverse-mutation assay (Ames test) with and without S9 metabolic activation; negative for the induction of micronuclei in both non-activated and S9-activated test systems in the in vitro mammalian cell micronucleus test using TK6 cells (proficient p53 human lymphocytes) and negative in the in vivo mouse micronucleus assay.

Collectively there were no findings observed during any of the nonclinical studies that would preclude testing of APL-2 in humans. IVT administration did not lead to any drug-related changes at any of the doses tested. SC administration led to much higher systemic APL-2 levels and some kidney toxicity was noted at the two highest SC doses. Most of the findings following daily SC administration were concluded to be the result of the PEG domain, and since PEGylated proteins are often cleared through the kidney, the high-dose changes noted in the kidney with APL-2 are not unexpected due to the presence of PEG40 as part of the APL-2 molecule. Results from the preclinical toxicology program with APL-2 provide good assurance of the safety for the proposed dose of APL-2 in humans by the IVT route of administration. The dose proposed in this study is 15 mg/eye/injection.

4.1.4 Clinical Data

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 age-related macular degeneration under protocol POT-CP043014 (NCT02461771), and the draft clinical study report is available. The study was conducted in multiple ophthalmological clinical sites in the US and Australia. A single dose of APL-2 was administered on Day 1 to patients suffering from exudative AMD currently receiving anti-VEGF (vascular endothelial growth factor) 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 serious adverse events (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 well-tolerated.

4.2 Rationale

4.2.1 Rationale for Doing this Study

The rationale for the use of a complement inhibitor in patients with AMD is based on evidence from both human and animal studies. Human biochemical, genetic, and clinical lines of evidence indicate that the complement system plays a role in the etiology of age-related

macular degeneration (AMD). Complement components including C3, the Membrane Attack Complex (MAC), and Complement Factor H (CFH), are present in drusen and basal laminar deposits in eyes from patients with AMD.[9,10,11,12] Genetic variants of CFH,[10,13,14,15,16] C3,[17,18] Complement Factor I (CFI)[19] and other complement components[20,21,22] have been associated with altered risks for the development of both the exudative and atrophic forms of AMD. Patients with AMD also have signs of systemic complement activation, exhibiting higher serum levels of Complement Factor B (CFB), C3a, C5a, SC5b-9, C3d, and Ba compared to age-matched controls.[23,24,25,26]

While there is not yet an anti-complement therapy approved for the treatment of exudative AMD or GA, data from recent clinical studies support the hypothesis that complement inhibition might have an effect on the etiology of age-related macular degeneration. In the Phase I clinical study, ASaP (Potentia Pharmaceuticals, Inc), thinning of the retina occurred in two high dose patients after treatment with the C3 complement inhibitor APL-1 (a.k.a. POT-4 /AL-78898A) despite extensive pre-existing retinal damage and resistance to anti-VEGF therapy.[27] Data from the Phase II clinical study Mahalo (Genentech Inc.), provides for the first time evidence of the positive effect of a complement inhibitor (lampalizumab; an anti-factor D molecule) in GA. The study showed that in the subpopulation of GA patients positive for a Complement Factor I (CFI) exploratory biomarker and treated monthly with lampalizumab, GA progression rate decreased by 44% over 18 months.[28,29]

In the current clinical study a complement C3 inhibitor, APL-2, will be administered to patients with GA. The goal of the study is to assess the safety and tolerability, and to obtain evidence of activity of IVT APL-2 administered monthly or EOM. Results from this study will guide decisions to further develop APL-2 for GA.

4.2.2 Dose Selection

A single dose of 15 mg/100 µL injection administered monthly or EOM for 12 months will be tested in this study (see Section 7.3.1). APL-2 was well-tolerated in a panel of animal toxicology studies. A 9-month, repeat-dose GLP study in cynomolgus monkeys was conducted to evaluate the safety of IVT injections of APL-2 at doses up to 24.8 mg/eye at a frequency of one injection every 4 weeks.

In this pivotal chronic toxicological study conducted in monkeys, the No-Effect-Level (NOEL) was established as >24.8 mg of APL-2 delivered intravitreally every 4 weeks for 9 months using a 100 µL injection. The volume of the human vitreous is approximately 4 mL, which is approximately 2.7-fold larger than the mean vitreous volume of cynomolgus monkeys, 1.5 mL.[30] Based on the difference in vitreous volume between man and cynomolgus and the NOEL defined in non-human primates, the human equivalent dose was determined to be 67 mg/eye every 4 weeks. The dose (15 mg/injection) of APL-2 that will be evaluated in this clinical study is expected to result in drug concentrations approximately 4.5 fold lower that the NOEL observed in cynomolgus monkeys.

4.3 Risk/Benefit

The safety monitoring practices employed by this protocol (e.g. complete ophthalmological exam, IOP monitoring, OCT, vital signs, hematology, serum chemistry, urinalysis, 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. IOP will be carefully monitored in this study.

The approximately 150 mL of blood (See Section 9.9) planned for collection from each subject over the 18 months of the study does not pose an undue risk in this patient population.

Based on data available to date, IVT administration of complement C3 inhibitors does not seem to present an unreasonable ophthalmic or systemic risk to humans. In three previous clinical studies involving 72 subjects undergoing local C3 inhibition with the related compound POT-4/AL-78898A, no drug-related SAEs were reported. Also, a Phase I study with APL-2 in patients with wet AMD has completed and no drug-related SAEs have been reported thus far.

Following a routine scheduled interim review of this ongoing POT-CP121614 (FILLY) study, including data as of April 5, 2017, by the Safety Monitoring Committee, an imbalance in new exudation in subjects treated with APL-2 was observed (further details described in an Investigator Brochure Addendum No. 3, 10 April 2017). Higher rates in new exudation were observed in eyes treated with APL-2, particularly monthly. The risk of developing new exudation may be increased in patients with a prior history of exudative AMD in the fellow eye. Visual acuity in subjects who develop new study eye exudation does not appear to differ significantly from those who do not.

There is a potential health benefit for trial participants from receipt of study drug. We propose to administer APL-2 to patients with GA. If efficacious, APL-2 is expected to alter the course of GA and slow its rate of growth.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1 Study Objectives

The primary objectives of the study are to assess the safety, tolerability and evidence of activity of multiple IVT injections of APL-2 in subjects with GA associated with Age-Related Macular Degeneration in order to support further development into confirmatory Phase III studies.

5.2 Study Endpoints

5.3 Primary Efficacy Endpoint

To demonstrate superiority of monthly and EOM APL-2 IVT injections compared to sham injections based upon the mean change in GA lesion size as measured by FAF.

- The primary endpoint is the change in square root GA lesion size from baseline to Month 12 as measured by FAF.

5.4 Primary Safety Endpoint

- Number and severity of local and systemic treatment emergent adverse events

5.5 Secondary Endpoints

Comprehensive but not limiting lists of secondary efficacy, safety and pharmacokinetic endpoints are presented in the Synopsis, Section 1.

6. PATIENT POPULATION

The study population includes approximately 240 subjects to be enrolled at approximately 40 multinational sites. To participate in the study, subjects must be diagnosed with GA of the macula associated with AMD in one or both eyes. If both eyes meet the criteria and qualify for the study, the eye with the worst visual acuity at the screening visit will be designated as the study eye. If both eyes have the same visual acuity, the right eye will be used as the study eye. The complete inclusion and exclusion criteria are presented in the Synopsis, Section 1.

6.1 Women of childbearing potential:

WOCBP are defined as pre-menopausal women physiologically capable of becoming pregnant.

6.2 Women non-childbearing potential:

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.

6.3 Approved methods of contraception

Approved methods of contraception include: oral contraceptives, intrauterine device, medically acceptable barrier methods (i.e. condom), implantable or injectable contraceptives or removable birth control device. Subjects practicing abstinence and coitus interruptus (pull out method) must agree to use an approved method of contraception during the study.

7. TREATMENT OF SUBJECTS

7.1 Allocation to Treatment

Each subject will be assigned a unique screening number before screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be scheduled to enter the study and randomized on Day 0 in a 2:2:1:1 manner to receive treatment with APL-2 Monthly (AM), APL-2 Every-Other-Month (AEOM), Sham injection Monthly (SM) or Sham injection Every-Other-Month (SEOM), respectively. The randomization scheme will be generated and maintained by the Sponsor. The randomization schedule will be blocked to ensure a balance of study treatment allocations within investigational sites.

7.2 Masking and Minimization of Bias

The intent of masking is to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of the clinical study. Bias could arise from the influence that the knowledge of a specific treatment assignment may have on the recruitment and allocation of subjects, their subsequent care, the assessment of end points, the handling of withdrawals, and so on. The essential aim of masking, therefore, is to prevent identification of the treatments by the subject and the masked assessors associated with the conduct of the study until all such opportunities for bias have passed.

This single-masked study is subject-masked and assessor masked, with subjects randomized to either APL-2 or Sham Injection, as well as to a monthly or EOM treatment schedule for 12 months. To prevent bias in treatment assignment, eligible patients will be randomized using a web-based randomization system. The subject and assessors (photographer(s) and visual acuity technicians) will be masked to the specific treatment being administered. The Investigators (including Sub-Investigators), site personnel not performing assessments of efficacy variables (imaging and visual acuity), vendors and Sponsor (or Contract Research Organization (CRO)) personnel will be unmasked to treatment assignment. Additionally, a masked independent review of SD-OCT, FAF, DCFP and FA images will be performed at the CRC to provide an objective assessment of these evaluations.

This level of masking will be maintained throughout the conduct of the study. In the event of a medical emergency where the knowledge of subject treatment by masked individuals (e.g. the subject or his/her physician) is required, an individual Investigator will have the ability to unmask the treatment assignment for a specific subject and share that information with the appropriate parties. The Investigator must endeavor to notify the Sponsor prior to unmasking a subject. The independent SMC will be provided unmasked safety data for their safety assessment.

7.3 Treatments Administered

7.3.1 Dose Levels and Study Arms

A single dose of 15 mg APL-2/100 µL will be tested in this study. Subjects will receive multiple IVT injections as outlined in the table below

Treatment Arms
APL-2 15 mg/100 µL Monthly for 12 months (13 injections)
APL-2 15 mg/100 µL EOM for 12 months (7 injections)
Sham Monthly for 12 months (13 sham injections)
Sham EOM for 12 months (7 sham injections)

7.3.2 Drug supplies

7.3.2.1 Identity of Investigational Product

APL-2 will be supplied as a lyophilized powder in stoppered glass vials and should be stored at -20°C and according to the label. Lyophilized APL-2 must be reconstituted prior to the IVT injection. Specific instructions for preparing APL-2 for the IVT injection procedure are provided in the Manual of Procedures (MOP).

7.3.2.2 Accountability

APL-2 drug product will be provided to a designee at the study site and must be stored in a pharmacy or otherwise locked and secured, at temperature of -20 °C (i.e. frozen). The drug product supply is accessible only to those individuals authorized by the PI. The Sponsor will supply sufficient quantities of APL-2 drug product to allow completion of this study.

Designated study staff will provide the study treatments to the subjects in accordance with their assigned subject numbers and the randomization schedule. During the study, the receipt of the drugs supplied at the clinical site and of study treatment dispensation for each subject will be documented in drug accountability records. These drug accountability records are to be kept separate from the patient medical records and other source documents.

All used vials should be retained by the clinical site until drug accountability monitoring is performed and then returned to the Sponsor or designee, or destroyed per Sponsor instructions. At the conclusion of the study, any unused investigational product will be retained by the clinical site, returned to the Sponsor or designee, or destroyed per Sponsor instructions, and this will be documented in the drug accountability records.

7.3.3 Intravitreal APL-2 Administration

Subjects receiving active treatment will be administered a100 µL IVT injections of APL-2 using a 29G or 27G thin wall needle, at the discretion of the PI. Detailed instructions on drug preparation, pre-injection procedures, administration of APL-2, and post-injection procedures are provided in the MOP. The procedure for sham injection will be the same as that used for IVT injection until the actual injection; no actual injection will occur. Detailed instructions on sham injection procedures are provided in the MOP.

Clinic staff involved in the injection tray assembly, anesthetic preparation, and study drug preparation and administration will follow appropriate aseptic techniques to minimize the risk of potential adverse events associated with IVT injections (e.g. endophthalmitis).

To minimize IOP elevation after IVT injection of APL-2, decompression of the eye must be performed before all APL-2 injections. This is done by applying moderate pressure to the globe with cotton swabs for 30-60 seconds during anesthetic preparation.[31]

In addition to the procedures outlined in the MOP, adherence to specific institutional policies associated with IVT injections will be observed.

7.4 Concomitant Therapies

Any concomitant medications a participant is receiving at the start of the study 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 CRF including start and stop date and time, dose, route, and indication. In addition, all ocular and non-ocular procedures such as surgical procedures (excluding study treatment procedures) 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.

7.4.1 Endophthalmitis Treatment

The decision to treat a participant for endophthalmitis or suspected endophthalmitis will be guided by the clinical judgment of the PI. 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.

8. STUDY PROCEDURES

8.1 Study Design

This is a Phase II, prospective, multicenter, randomized, single-masked, sham-controlled study to assess the safety, tolerability and evidence of activity of multiple IVT injections of APL-2 in subjects with GA associated with Age-Related Macular Degeneration.

Patients diagnosed with GA associated with age-related macular degeneration in the study eye and who meet all inclusion/exclusion criteria will be included in the study. The study will randomize approximately 240 subjects to obtain at least 200 evaluable subjects across 40 multinational sites.

Patients should be screened 14 (±5) days before receiving APL-2. Upon entry into the study, patients will be assigned a subject screening number. Subjects who meet all inclusion and exclusion criteria and are confirmed as eligible by the CRC will return to the clinic for the randomization visit (Day 0) and randomized as outlined in Section 7.1.

All subjects will return to the clinical site on Day 7 to assess acute safety after the first injection. After that, subjects in the monthly groups will return to the clinical site for additional APL-2 (or

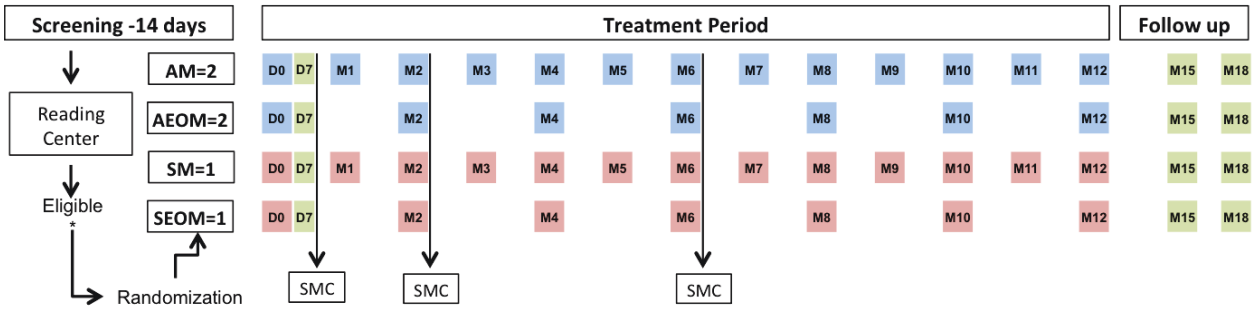
Sham) injections and study procedures every month until Month 12. Subjects in the EOM groups will return to the clinical site for additional APL-2 (or Sham) injections and study procedures every two months until Month 12. All subjects will return for follow-up visits 3 and 6 months after Month 12 (Months 15 and 18, respectively)

Subjects who discontinue study treatment, can continue participation in the study and return to the clinical site for their scheduled study procedures (with the exception of APL-2/Sham administration).

Subjects who fully withdraw from the study before Month 12, should complete the Termination Visit.

See Study Outline below.

Study Outline



AM = APL-2 Monthly. SM = Sham Monthly. AEOM = APL-2 Every-Other-Month. SEOM = Sham Every-Other-Month. D = Day. M = Month.
SMC = Safety Monitoring Committee. SMC will review cumulative safety data after the first 20 subjects have completed Day 7, Month 2 and Month 6 visits.
* Eligibility to be confirmed by Central Reading Center.

Safety will be assessed throughout the study; serial blood samples and urine samples will be collected. Blood samples will also be collected for the PK assessment of APL-2.

The planned length of participation in the study for each subject is approximately 18.5 months (from Day –14 through completion of the Month 18 (Day 540) follow-up procedures).

The study is planned to take place over approximately 28 months (from screening of the first subject through completion of the last subject's exit visit).

8.2 Safety Monitoring Committee

An external, independent Safety Monitoring Committee (SMC) will review cumulative unmasked safety data and will have the responsibility to conduct a thorough safety assessment after the first 20 subjects have completed the Day 7, Month 2 and Month 6 visits. A key responsibility of the SMC will be to make a recommendation whether to continue, modify or stop the study based upon an evaluation of emerging safety data, in particular Adverse Events of Special Interest as outlined in Section 10.1.3. Additional regular or ad-hoc safety reviews will be scheduled as recommended by the SMC.

8.3 Study Visit Schedule

Below is a condensed description of the study visits and the procedures and examinations that will be performed. Please refer to the Study Flow Charts in Section 2 for a detailed schedule of procedures/assessments for the Monthly and EOM visit schedules. Additional safety assessments not listed in section 8.3 or the flow chart may be performed if considered necessary at the discretion of the PI.

8.3.1 Screening – Within 14 days prior to treatment

Visit 1 - All subjects

All ophthalmic procedures (including imaging) are to be performed on **both eyes**

1. Before any study specific procedures are performed, explain the purpose and nature of the study, and have the patient read, sign, and date the Institutional Review Board/Independent Ethics Committee (IRB/IEC)-approved Informed Consent Form (ICF). Have the individual obtaining consent from the patient and a witness, if applicable, sign and date the ICF.
2. Obtain a screening number for the subject.
3. Obtain information on demographics, medical/ocular history, and concomitant medications used 90 days prior to enrollment. Include vitamins, and all over-the-counter as well as prescription medications.
4. Screen the patient for inclusion/exclusion criteria.
5. Collect blood (including blood for HCG/FSH/LH, if applicable) and urine for laboratory analysis and forward the samples to the central laboratory.
6. Collect blood for PK and anti-APL-2 antibody analysis.
7. Collect vital signs.
8. Perform BCVA.
9. Perform LL-BCVA.
10. Perform a complete ophthalmic exam including slit-lamp exam of the cornea, iris, anterior chamber, lens (LOCS III if any opacity on the lens noted) and aqueous reaction (cells and flare), dilated fundus exam of the vitreous and retina and IOP measurement.
11. Perform SD-OCT imaging and forward the images to the CRC for determination of eligibility.
12. Perform FAF imaging and forward the images to the CRC for determination of eligibility.
13. Perform IR imaging (if applicable) and forward the images to the CRC.
14. Perform DCFP and forward images to the CRC for determination of eligibility.
15. Perform FA and forward the images to the CRC for determination of eligibility.

8.3.2 Initial Treatment – Day 0 – Within 14 Days of screening

Visit 2 – All groups

Unless specified, all ophthalmic procedures (including imaging) are to be performed on the **study eye only.**

1. Verify that all inclusion/exclusion criteria are met, including the determination of eligibility by the CRC.
2. Obtain information on any changes in medical health and/or the use of concomitant medications.
3. Collect vital signs pre- and post-dose. Vital signs will be measured within approximately 1 hour prior to dosing for the pre-dose time point. Post-dose vital signs readings will be performed within 30 minutes after dosing.
4. Perform BCVA.
5. Perform LL-BCVA.
6. Perform a complete ophthalmic exam including slit-lamp exam of the cornea, iris, anterior chamber, lens (LOCS III if any opacity on the lens noted) and aqueous reaction (cells and flare), dilated fundus exam of the vitreous and retina and IOP measurement.
7. Use Interactive Web Response (IWR) for subject randomization
8. Perform the IVT injection of APL-2 (or Sham injection) as described in the MOP.
9. Monitor the study eye within 15 minutes post injection as outlined in Section 9.8 and in the MOP.
10. Monitor for adverse events.

8.3.3 Post initial treatment examination - Day 7 –

Visit 3 – All groups

Unless specified, all ophthalmic procedures (including imaging) are to be performed on the **study eye only.**

1. Obtain information on any changes in medical health and/or the use of concomitant medications.
2. Collect vital signs.
3. Collect blood for PK analysis.
4. Perform BCVA.
5. Perform LL-BCVA.
6. Perform a complete ophthalmic exam including slit-lamp exam of the cornea, iris, anterior chamber, lens (LOCS III if any opacity on the lens noted) and aqueous reaction (cells and flare), dilated fundus exam of the vitreous and retina and IOP measurement.

7. Monitor for adverse events.

8.3.4 Injection Visits – Monthly or EOM until month 12 -

Monthly Groups: Days 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330 and 360 - Visits 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15, respectively.

EOM Groups: Days 60, 120, 180, 240, 300 and 360 – Visits 4, 5, 6, 7, 8 and 9 respectively.

Unless specified, all ophthalmic procedures (including imaging) are to be performed on the **study eye only**. The following procedures will be performed at all injection visits:

1. Obtain information on any changes in medical health and/or the use of concomitant medications.
2. Collect vital signs pre- and post-dose. Vital signs will be measured within approximately 1 hour prior to dosing for the pre-dose time point. Post-dose vital signs readings will be performed within 30 minutes after dosing.
3. Collect blood for PK analysis.
4. Perform urine pregnancy test before APL-2 injection. -**WOCBP only-**
5. Perform BCVA. **-Both eyes on Day 360 only-**
6. Perform LL-BCVA. **-Both eyes on Day 360 only-**
7. Perform a complete ophthalmic exam including slit-lamp exam of the cornea, iris, anterior chamber, lens (LOCS III if any opacity on the lens noted) and aqueous reaction (cells and flare), dilated fundus exam of the vitreous and retina and IOP measurement.
8. Perform the IVT injection of APL-2 (or Sham injection) as described in the MOP.
9. Monitor the study eye within 15 minutes post-injection as outlined in Section 9.8 and in the MOP.
10. Monitor for adverse events.

The following procedures will be performed only at specific visits, as noted:

1. Collect blood and urine for laboratory analysis and forward the samples to the central laboratory. - **Only on Days 60, 180 and 360 for all groups -**
2. Collect blood for genetic marker analysis (if applicable, see Section 9.3) and forward the samples to the central laboratory. - **Only on Days 60 for all groups -**
3. Perform SD-OCT imaging and forward the images to the CRC. - **Only on Days 60, 180 and 360 for all groups -**
4. Perform FAF imaging **of both eyes** and forward the images to the CRC. - **Only on Days 60, 180 and 360 for all groups –**
5. Perform IR imaging (if applicable) **of both eyes** and forward the images to the CRC. - **Only on Days 60, 180 and 360 for all groups -**

8.3.5 Follow up visit - Day 450 -

Visit 16 and 10 for Monthly and EOM, respectively

Unless specified, all ophthalmic procedures are to be performed on the **study eye only**.

1. Obtain information on any changes in medical health and/or the use of concomitant medications.
2. Collect blood for PK analysis.
3. Collect vital signs.
4. Perform urine pregnancy test. -**WOCBP only-**
5. Perform BCVA.
6. Perform LL-BCVA.
7. Perform a complete ophthalmic exam including slit-lamp exam of the cornea, iris, anterior chamber, lens (LOCS III if any opacity on the lens noted) and aqueous reaction (cells and flare), dilated fundus exam of the vitreous and retina and IOP measurement.
8. Monitor for adverse events.

8.3.6 Termination Visit (or Early Termination) – Day 540 -

All ophthalmic procedures are to be performed on **BOTH EYES**.

1. Obtain information on any changes in medical health and/or the use of concomitant medications.
2. Collect blood and urine for laboratory analysis and forward the samples to the central laboratory.
3. Collect blood for PK analysis.
4. Collect vital signs.
5. Perform urine pregnancy test. -**WOCBP only-**
6. Perform BCVA.
7. Perform a complete ophthalmic exam including slit-lamp exam of the cornea, iris, anterior chamber, lens (LOCS III if any opacity on the lens noted) and aqueous reaction (cells and flare), dilated fundus exam of the vitreous and retina and IOP measurement.
8. Perform SD-OCT imaging and forward the images to the CRC.
9. Perform FAF imaging and forward the images to the CRC
10. Perform IR imaging (if applicable) and forward the images to the CRC.
11. Perform DCFP imaging and forward images to the CRC.
12. Perform FA imaging and forward the images to the CRC.
13. Monitor for adverse events.

8.3.7 Unscheduled Visit

If a subject returns to the clinical site before their next scheduled visit for an assessment of an adverse event or at the request of the PI, all assessments completed at the Unscheduled Visit should be documented in the patient source record and in the eCRF.

9. ASSESSMENTS

The following evaluations will be performed during the study as outlined in the Study Flow Charts in Section 2. Refer to the MOP for detailed descriptions of study-related procedures.

9.1 Vital signs

Vital signs consist of body temperature, respiratory rate, blood pressure, and heart rate measurements. Standardized procedures for each are provided in the MOP.

On injection visits, vital signs will be measured within approximately 1 hour prior to dosing and within 30 minutes after dosing.

Vital signs will be measured before venipuncture.

9.2 Laboratory analysis of blood and urine

Collection of blood and urine will occur at the study site and the samples will be shipped to a central laboratory for analysis. A standardized procedure for the collection and processing of blood and urine is provided in the MOP.

The following clinical labs will be performed:

Hematology

- Hemoglobin
- Hematocrit
- Red blood cell (RBC) count
- Platelet count
- White blood cell (WBC) count with differential

Chemistry

- Blood urea nitrogen (BUN)
- Creatinine
- Bilirubin (total, direct and indirect)
- Albumin
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Creatine kinase
- Glucose
- Electrolytes (sodium, potassium, chloride, bicarbonate)

Urinalysis

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

Complement

- C3
- CH50

Other

- Human chorionic gonadotropin (HCG) [a]
- Follicle-stimulating hormone (FSH) [b]
- Luteinizing hormone (LH) [b]

The Investigator must review the results of the Screening Visit clinical laboratory tests (including recheck results) and confirm that these results do not show evidence of any medical condition that would make study participation inappropriate. The Investigator should also assess any changes from baseline at the follow up visits and the Exit Visit.

Notes:

- Serum Pregnancy Test (i.e. HCG) will be performed for females of child bearing potential at screening only.
- FSH and LH will be performed for postmenopausal females at screening only.

9.3 Genotyping Samples

The genetic marker sample will be used to evaluate the relationship between genetic polymorphisms associated with AMD with disease progression and response to APL-2.

A whole-blood sample will be collected for genetic marker analysis at the Day 60 visit. These samples will be required for all subjects with the exemption of clinical sites located where prohibited by law, clinical sites with policies in place that prohibit collection of samples for genetic marker testing and clinical sites were IRB/IEC has not approved genetic testing.

9.4 Urine pregnancy test

Urine pregnancy test will be performed in WOCBP only as outlined in the Study Flow Chart in Section 2.

9.5 Best-corrected visual acuity

Best-corrected visual acuity (including LL-BCVA) testing, performed by a certified VA examiner, should precede any examination requiring administration of eye drops to dilate the eye or any examination requiring contact with the eye. Best-corrected visual acuity should be performed following refraction and completed according to the procedures outlined in the MOP.

9.6 Complete ophthalmic exam

The complete ophthalmic exam will consist of the following:

- External examination of the eye and adnexa.
- Routine screening for eyelids/pupil responsiveness (including ptosis, abnormal pupil shape, unequal pupils, abnormal reaction to light and afferent pupillary defect).
- Slit-lamp examination [cornea, anterior chamber, iris, lens, aqueous reaction (cells and flare). Grading scales are outlined in the MOP. If an abnormal lens finding is noted during

the slit-lamp examination, at any visit, then the finding should be further characterized with LOCS III. All subsequent visits for that subject should include LOCS III. A complete description of LOCS III standardized procedures and grading scales is outlined in the MOP.

- Dilated fundus exam including evaluation of retina and vitreous (i.e. posterior segment abnormalities, retinal hemorrhage/detachment, and vitreal hemorrhage density and vitreous cells). Vitreal hemorrhage density and vitreous cells grading scales are outlined in the Manual of Procedures.
- IOP measurement - A measurement of intraocular pressure will be conducted using Tono-pen, iCare or Goldmann applanation tonometer as outlined in the MOP. The same method should be used for all measurements in the same subject throughout the study.

9.7 Ocular Imaging

The following ocular images will be obtained and sent to the CRC as outlined in the visit schedule in Section 8.3. Also see Study Flow Charts in Section 2.

- Digital Color Fundus Photographs
- Fluorescein angiography
- Spectral Domain Optical coherence tomography
- Fundus Autofluorescence
- Infrared reflectance imaging. Only done at selected clinical sites with Heidelberg Spectralis® system.

A standardized procedure for the collection of each imaging modality is provided in the CRC manual/s. Certification of the equipment and examiners for all imaging modalities at each investigative site will occur prior to any evaluation of study subjects.

9.8 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) and monitoring IOP. If subject passes gross vision test and IOP is < 30 mmHg, the subject may leave the site. If subject fails gross vision test **and/or** IOP is > 30 mmHg, assessments will continue every approximately 30 minutes until the subject passes gross vision test and IOP is < 30 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.

9.9 Blood Volume for Study Assessments

Blood Volume during Study (up to Day 113)

Assay	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Pharmacokinetics	10/16	4	40/64
Anti-APL-2 Antibodies	10/16	4	40/64
Hematology	5	4	20
Chemistry (Incl. HCG/LH/FSH)	5	8.5	42.5
Genotyping Sample	1	2	2
Complement profile (C3, CH50 and Total complement)	4	4	16
		Total Blood Volume for Study	160.5/208.5

Note: Number of samples (and volumes) for certain assays differ for Monthly vs EOM groups and are expressed as M/EOM.

10. ADVERSE EVENTS

All adverse events (AEs) (as defined in Section 10.1), either observed by the PI or one of their medical collaborators, or reported by the participant spontaneously, or in response to direct questioning, will be reported. All adverse events (ocular, non-ocular, serious, non-serious, volunteered, and elicited) must be documented in study records.

10.1 Definitions

10.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a subject who receives a pharmaceutical product. The occurrence does not necessarily have to have a causal relationship with the treatment. Therefore, an AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a drug, whether or not considered related to the drug.

Note:

- For purposes of this study, abnormal laboratory values will not be considered adverse events unless deemed clinically significant by the Investigator. All abnormal laboratory values will be recorded in the database and appropriate analyses presented in the final study report.

10.1.2 Serious Adverse Event

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening: this means that the subject was at risk of death at the time of the event; it does not mean that the event might have caused death had it occurred in a more severe form;
- Required hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
- Is a congenital anomaly or 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.

Medical and scientific judgment should be exercised in deciding if an AE is serious and if expedited reporting is appropriate.

10.1.3 Adverse Events of Special Interest

An adverse event of special interest is one of scientific and medical concern specific to the Sponsor's product or program where ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. These adverse events may be serious or non-serious. Applicable adverse events may require further investigation in order to characterize and understand them, and depending upon the nature of the event, rapid communication by the trial Sponsor to other parties may also be required. These adverse events of special interest must be reported using the same mechanism and timeframe (i.e. within one working day of the Investigator's or delegate's knowledge of the event) as described for serious adverse events in Section 10.3. The adverse events of special interest include the following:

- Endophthalmitis
- 4+ ocular inflammation
- 2-3+ ocular inflammation that fails to decrease to 1+ or less within 30 days of the onset of the event
- Sustained (> 5 minutes) loss of light perception after APL-2 injection
- Sustained elevation of IOP (30 mmHg) at/past 90 minutes post-injection
- Any elevation of IOP requiring surgical intervention (i.e. paracentesis)
- New vitreous hemorrhage of > 2+ severity that does not resolve within 14 days of the onset of the event
- Progression to exudative AMD in the study eye or fellow eye requiring **surgical** intervention (see note below).

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

Note: Intravitreal administration of anti-VEGF agents are **not** considered surgical interventions.

10.2 Adverse Event Assessment and Recording

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. For each AE, the PI should note the start and resolution dates, the severity, whether it meets the definition of an SAE (see Section 10.1.2), 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.

When reporting an adverse event, the event description should use the best matching terminology describing the event as found in the "Common Terminology Criteria for Adverse Events" (CTCAE, v 4.03). If an available CTCAE term fits the event well, no additional descriptors may be needed. However, the Investigator should add any necessary descriptions in order to clarify the event or to place it in an appropriate context. If an appropriate term matching the adverse event cannot be found in the CTCAE and you do not know the preferred MedDRA term, the adverse event description should include a diagnosis, sign or symptom with additional information to facilitate subsequent categorization into MedDRA coding terms.

10.2.1 Intensity

The PI must grade the severity of all reported adverse events into one of five categories: Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Life-Threatening) or Grade 5 (Death related to AE). The standardized CTCAE severity grading scales for the specific type of adverse event reported must be used when a matching CTCAE term is available. If no reference to a standard grading scale applies or is immediately available, use the following guideline:

10.2.1.1 Grade 1—Mild

Persistence of any otherwise insignificant medical occurrence beyond 72 hours or any transient (< 72 hours) AE considered by the PI to be related to the study drug. No or minimal medical therapy or intervention required, hospitalization not necessary, no or little limitation in normal activities; nonprescription or single-use prescription therapy may be employed to relieve symptoms. Mild adverse events may be listed as expected consequences of the therapy for any given protocol, and standard supportive measures for such an expected event do not necessarily elevate the event to a higher grade.

10.2.1.2 Grade 2—Moderate

Mild to moderate limitation in activity, some assistance may be needed; possibly none but usually minimal intervention/therapy required, hospitalization possible.

10.2.1.3 Grade 3—Severe

Marked limitation in activity, some assistance usually required; medical intervention/therapy required; hospitalization possible or likely. [Specifically for ocular adverse events in this vision-related study, an immediately sight-threatening condition (e.g., impending corneal perforation, retinal detachment) may be categorized as Grade 3 if it would lead to total blindness in the affected eye(s).]

10.2.1.4 Grade 4—Life-Threatening

Extreme limitation in activity, significant and immediate assistance required; significant medical/therapy intervention required to prevent loss of life; hospitalization, emergency treatment or hospice care probable. This grade is used when the participant was, in the view of the PI, at substantial risk of dying at the time of the adverse event or it was suspected that use or continued use of the test article would have resulted in the participant's death. (This does not include a reaction that, had it occurred in a more serious form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.)

10.2.1.5 Grade 5 – Death

Death related to AE.

10.2.2 Causality

The PI (or an authorized study physician) must submit an attribution for causality of the reported adverse event to the test article or procedure.

The attribution should take into account both the temporal association and any known physical, physiological or toxicological information regarding the test article that could reasonably infer causality. Causality should only be considered for the experimental test article and not for any standard study examination or diagnostic procedures. The four attribution categories are:

Unrelated	Does not follow a reasonable temporal sequence from the administration of study drug. The event or laboratory test abnormality is clearly due to extraneous causes (disease, other drugs, environment, etc.).
Unlikely Related	Does not follow a known pattern of response to study drug. Does not follow a reasonable temporal sequence from the administration of study drug. Disease or other drugs provides plausible explanation. It does not reappear or worsen when study drug is re-administered.
Possibly Related	Follows a known pattern of response to study drug. Time sequence from administration of the study drug is reasonable. Could also be explained by disease or other drugs.
Probably Related	Follows a known pattern of response to study drug. Time sequence from administration of the study drug is reasonable. Response to withdrawal clinically reasonable. Cannot be reasonably explained by the known characteristics of the participant's clinical state, environmental factors, or other therapies administered to the subject.

10.3 Serious Adverse Event Reporting

All SAEs (defined in Section 10.1.2), whether judged related or not to study medication, will be reported to the Sponsor (or designated Medical Monitor) by telephone, e-mail or facsimile within

24 hours of the Investigator becoming aware of such SAEs. Contact information and instructions for completing SAE forms are provided in the MOP.

The initial SAE Report should include, at a minimum, the following information:

- Protocol number (POT-CP121614)
- Site number
- Subject screening number, initials, gender, and date of birth
- Name of PI and investigator site address
- Details of SAE
- Criterion for classification as "serious"
- Date of SAE onset

Follow-up SAE reports should be submitted as further information becomes available, and the final SAE Report should include information on the SAE intensity, outcome, and relationship to study drug; dates of study drug administration, concomitant medications, and any other relevant information. The PI should also provide clear copies of supporting documents as necessary (e.g. hospital discharge summary, laboratory reports, autopsy reports, etc), with the subject's personal identifiers removed. All SAEs will be followed until the acute event has resolved, even if the subject discontinues study participation prior to the resolution. The Investigator must report SAEs occurring at his/her site to the IRB/IEC as required.

10.4 Expected Adverse Events

10.4.1 Expected AE related to the test article

No ocular or systemic AE related to the test article are expected at the doses proposed in this protocol.

10.4.2 Expected AE related to the IVT injection procedure

Mild discomfort related to the injection procedure (including use of an eyelid speculum, anesthetic drops, mydriatic drops, antibiotic drops, povidone-iodine drops or flush and subconjunctival injection of anesthetic, as well as the actual insertion of the IVT needle) are expected. These procedure-related adverse events include but are not limited to: redness, mild eye pain, eye irritation, visual disturbance, abnormal sensation in the eye, etc. and will be graded as indicated in Section 10.2.1.

10.5 Disease Progression

A condition considered by the PI as unequivocal AMD disease progression, such as lesion growth, lesion bleeding, lesion that exudes fluid, an RPE tear, and extensive deposition of lipid, in the study eye or fellow eye should be identified as such in the participant's source documents. Disease progression that requires an intervention (e.g. administration of IVT anti-VEGF agents) should be recorded as an adverse event in the CRF. If an intervention is not required the progression is not considered an AE. The unequivocal nature of the disease progression must be indicated in the source documents. Normal progression or worsening of the medical condition under study (e.g. vision loss due to the progression of AMD), by itself, does not necessarily constitute an adverse event unless the change can be reasonably attributed to an action of the test article and not only to its lack of efficacy.

Disease progression to exudative AMD in the study eye or fellow eye requiring **surgical** intervention should be reported as an AESI (See Section 10.1.3). Anti-VEGF agents are **not** considered surgical interventions.

10.5.1 Withdrawal

Participants may choose to discontinue from treatment or to completely withdraw from this study for any reason at any time without penalty or prohibition from enrolling in other clinical protocols.

Participants wishing to withdraw from the study completely will be offered an early termination visit. This early termination visit will include the examinations outlined in Section 8.3.6.

Participants wishing to discontinue treatment but willing to continue with other study procedures, will return to the clinical site for follow-up visits, as per protocol, every month or every two months until Month 12 and then Month 15, and a Termination Visit at Month 18.

10.6 Pregnancy in the Clinical Trial

Women of childbearing potential (WOCBP) are not excluded from the study as long as adequate birth control methods are being utilized. Prior to enrollment in the clinical trial, WOCBP must be advised of the importance of avoiding pregnancy during the trial and the potential risks associated with an unintentional pregnancy. WOCBP and males with partners who are WOCBP will be instructed to practice an acceptable method of birth control (as defined in Section 6.3) for the duration of the study. Male subjects will be counseled to avoid donating sperm after dosing on Day 1 until the final Exit visit.

During the trial, female subjects are to be instructed to contact the Investigator immediately if they suspect they might be pregnant. The study Sponsor must be contacted immediately and a decision will be made regarding continuation of the pregnant woman in the study based upon the circumstances surrounding the pregnancy. Pregnancy is not reportable as an adverse event; however, complications may be reportable. If a female subject or partner of a male subject becomes pregnant during the study, the PI should report the pregnancy to the Medical Monitor within 24 hours of being notified. The Investigator should follow the pregnancy until completion. At the completion of the pregnancy, the Investigator 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 Investigator should follow the procedures for reporting an SAE.

11. STATISTICAL CONSIDERATIONS

Analyses planned during the study include: 1) a primary intention to treat efficacy analysis after all subjects are randomized and complete 12 month follow up; and 2) ancillary analyses which will be conducted on 6 month follow up data and per-protocol analyses at both time points.

All statistical tests will be two-sided with a type 1 (alpha) error rate of 0.1. To understand the clinical significance of the estimated treatment effects and to aid in the interpretation of the formal hypothesis testing, two-sided 95% confidence intervals will be provided.

Descriptive summaries will include mean, standard deviation, median, and range for continuous variables and counts and percentages for categorical variables.

11.1 Populations for analysis

11.1.1 Primary Efficacy Analysis

The primary efficacy analysis will be based on a modified intention-to-treat population (mITT), which is defined as all randomized subjects who receive at least one dose of treatment and have at least one visit at or after month 2. Month 2 is the first visit on treatment at which lesion area is measured.

11.1.2 Supportive Efficacy Analyses

Per protocol (PP) efficacy analyses will include all randomized subjects who return for 12 (or 6) months of follow up.

11.1.3 Safety Analysis

All subjects who are randomized and receive at least one dose of treatment will be included in the evaluation of safety of APL-2. Patients will be grouped according to treatment received.

11.2 Statistical methods

11.2.1 Analysis of the Conduct of the Study

The number of subjects who enroll, discontinue (early discontinuation of treatment or early termination from the study), and complete the study (through 12 months after randomization) will be tabulated by group.

Reasons for early discontinuation of the treatment or early termination of from the study will be listed and summarized by treatment group. Any eligibility criteria exceptions and other protocol deviations will also be summarized by treatment group.

11.2.2 Analysis of Treatment Group Comparability

Demographic and baseline characteristics – such as age, gender, race, total lesion size, and baseline visual acuity score – will be summarized for all randomized subjects by treatment group.

11.2.3 Efficacy Analysis

The primary objective of this study is to determine if the mean annual growth of GA lesions in eyes injected with APL-2, either monthly (AM) or every other month (AEOM), is different from growth in eyes receiving sham injections (S). Growth will be assessed as change in square root lesion areas.[32,33]

11.2.3.1 Statistical Hypothesis

The null and alternative hypotheses for this study are:

H0: $\mu S = \mu AM = \mu AEOM$ vs HA: $\mu i = \mu j$ for $i \in \{S, AM\}$; $j \in \{AM, AEOM\}$ and where μ indicates each groups respective 12 month change in square root lesion area .

11.2.3.2 Analytic Methods

Since prior studies have demonstrated that square root area changes are independent of baseline size, [1, 2] we anticipate analysis with one factor Analysis of Variance (ANOVA) and no need for a baseline covariance correction or baseline size stratification. If the overall hypothesis of equality of group means (H_0) is rejected at the 0.1 alpha level, then group means will be compared with post-hoc Least Significant Difference (LSD) multiple comparisons. These multiple comparisons will also be conducted at the 0.1 alpha level.

11.3 Determination of Sample Size

The sample size required is based on the 12 month per protocol analysis. Thus drop out is accounted for in the sample size determination.

11.3.1 Natural history growth rates

Based on two assessments of GA growth measured with Cirrus OCT,[32,33] we assume that in the absence of treatment average square root area legion growth is 0.33mm/year (mean of 0.28mm/year[33] and 0.37mm/year[32]) and the standard deviation of annual square root area growth is 0.21mm/year.[32]

11.3.2 Treatment allocation

To preserve masking of subjects and assessors, sham injections will be randomly assigned to either a monthly (SM) or every other month (SEOM) arms, but the two sham groups will be pooled for hypothesis testing (S). Thus randomized treatment allocation will be AM: AEOM: SM: SEOM in a 2:2:1:1 fashion. As above, for analysis SM and SEOM will be pooled into a single group, S.

11.3.3 Treatment efficacy and power analysis

This study is designed to detect a 30% reduction in annual square root area increase. Calculations are provided for three scenarios (Proc Power onewayanova, SAS 9.3)

Square root area change (mm)			Sample size			
AM	AEOM	S	AM	AEOM	S	Power to detect a difference
0.23	0.23	0.33	67	67	67	91%
0.23	0.33	0.33	67	67	67	91%
0.23	0.28	0.33	67	67	67	83%

11.3.4 Drop out/Loss to follow up

We assume a 15-20% loss to follow up. Accordingly, inflation of the sample size in (d) Total N = 201÷83.5% suggests recruitment of 240 subjects should be sufficient.

11.4 Safety Assessment

Adverse events will be collected from the time of the first study drug administration until a subject completes the study or discontinues prematurely. A treatment-emergent adverse event is defined as any new adverse event reported or any worsening of an existing condition on or after the first dose of study drug. Treatment-emergent adverse events will be summarized by treatment group.

Adverse events will be summarized by MedDRA coding terms, and separate tabulations also will be produced for related adverse events (those considered by the PI as definitively drug related),

serious adverse events and discontinuations due to adverse events. Vital signs data and findings from physical and ophthalmologic examinations will be tabulated for changes over time on study. Laboratory parameters will be summarized for changes across study by using descriptive statistics.

11.5 Handling of Missing Data

All efforts will be made to minimize missing data. For the primary efficacy endpoint (12 month mITT), we will impute using the last observation prior to month 12. However, if there is an imbalance in loss to follow up by treatment group, we will employ a regression method of imputation. The reason for this is a scenario in which fewer subjects in the actively treated arms complete follow up. Use of their, for example, 2 month visit lesion areas in the efficacy analysis would artificially decrease the mean growth estimates in the actively treated groups.

11.6 Interim analyses

We do not plan a formal interim analysis and so have not adjusted alpha for one. The decision to pursue a phase III trial and the planning for it will be based on the one year follow up analysis. That is, while a six-month analysis may be performed, even a statistically significant effect would not result in discontinuation of the Phase II trial and implementation of a Phase III study.

11.7 Exploratory Efficacy Endpoints

Other variables used for efficacy analyses will include lesion growth measurements by SD-OCT and change in visual acuity (letters read).

11.8 Randomization

The methods for generating the randomization schedule and for assigning study subjects to treatment arms will be described in a separate Randomization Plan and Specifications Document and included in the MOP.

12. ETHICS

12.1 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations (21 CFR Parts 50, 56, and 312) GCP, the ethical principles set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

12.2 Institutional Review Board/Ethic Committee

The study protocol, any amendments to the protocol, ICF, 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.

The IRB/IEC must be constituted and operate in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56) and/or ICH Guidelines, or other local regulations as deemed appropriate.

12.3 Subject Information and Consent

The Investigator is responsible for obtaining an informed consent. A written informed consent, in compliance with the US Code of Federal Regulations (21 CFR Part 50) and/or ICH Guidelines, must be obtained from each subject prior to screening and enrollment or performing any study related procedures.

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. The subject will be given sufficient time to consider the study's implications before deciding to participate in the study. The subject and/or legal guardian will be required to sign and date an ICF and will be assured that they may withdraw from the study at any time without jeopardizing their medical care. The Investigator shall retain the original, signed ICF for study participation in the subject's medical record and shall provide the subject and/or legal guardian with a copy of the signed ICF.

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

12.4 Confidentiality

Confidentiality of subjects information must be maintained in accordance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule-Final Modification (45 CFR Parts 160 and 164), ICH Guidelines, and/or any other local guidelines and regulations.

13. ADMINISTRATIVE CONSIDERATIONS

13.1 Direct Access to Source Data/Documents

The Investigator 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 printed CRF pages that are used as the source.

The Investigator will permit trial-related monitoring, audits, and inspections by the Sponsor and/or its' designee, IRB/IEC, and the regulatory agencies at any time during the study. The Investigator 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.

13.2 Quality Control and Quality Assurance

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

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

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

13.3 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 Investigator will provide direct access to source data/documents for study-related monitoring. It is important that the Investigator and the Investigator Site 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 Investigator.

13.4 Data Handling and Record Keeping

The Investigator 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 2 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 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. All essential documents generated in connection with this study in Australia and New Zealand must be retained for at least 15 years after study completion. 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 Investigator/Institution as to when these documents no longer need to be retained.

13.5 Protocol Amendments

Any amendments to the study protocol deemed necessary as the study progresses will be discussed between Sponsor and the Investigator. The Investigator will not implement any changes to the protocol without an agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, 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 amendments will be made jointly between the Sponsor and the Investigator and must be confirmed in writing. Amendment(s) will be approved and signed off in the same way as the protocol.

13.6 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).

13.7 Finance and Insurance

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

13.8 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 Investigator and Site personnel by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

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

13.9 ClinicalTrials.gov

This study will be listed with ClinicalTrials.gov, as applicable.

13.10 Termination of Study

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

REFERENCES

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