Statistical Analysis Plan

Sponsor Name:	Apellis Pharmaceuticals, Inc.
Protocol Number:	POT-CP121614
Protocol 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 -
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Signature Page

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I confirm that I have reviewed this document and agree with the content.

Author

PPD

Date **(dd-Mmm-yyyy)**

Approvals

PPD

Date **(dd-Mmm-yyyy)**

Apellis Pharmaceuticals, Inc.

RATIONALE AND SUMMARY OF REVISION V3.0:

The Statistical Analysis Plan (SAP) V2.0 is revised for the following reasons:

- To add additional exploratory endpoints and analysis methods that are associated with 18-month data and addressing a different growth rate from visit to visit;
- To add additional summary tables and figures for the added exploratory endpoints, and to remove redundant summary tables;
- To clarify that all by-visit summaries and analyses of change from baseline over time for data up to Month 12 will be repeated to include all data up to Month 18 for the final analysis 18-month data;
- To revise the numbering and titles of the planned summary tables, listings and figures (TLFs) to match those specified in the TLF Shells documents and modified upon the pre-database-lock review of 12-month data; and
- Additional editorial changes across the document to improve clarity.

RATIONALE AND SUMMARY OF REVISION V2.0:

The Statistical Analysis Plan (SAP) is revised for the following reasons:

- To specify that the CSR will be based on the primary 12-month data cut. An addendum to the CSR will be generated with the final 18-month data;
- To move anterior and posterior segment examinations from efficacy sections to safety sections;
- To add a subgroup analysis of the primary endpoint by GA lesion size at baseline;
- To remove redundant summary tables;
- To change the comparison method from chi-squared test to Fisher's exact test for incidence of macular neovascularization to handle the situation of low incidence in any group;
- To specify that adverse events will be summarized separately for those occurs in the study eyes, in the fellow eye, and those that are non-ocular;
- To add the summaries for prior/concomitant medications used in the study eyes, and for those used in the fellow eyes;
- To modify the numbering and titles of the planned summary tables, listings and figures (TLFs) to match those specified in the TLF Shells documents; and
- Additional editorial changes across the document to improve clarity.

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
ACR	Albumin Creatinine Ratio
AE	Adverse Event
AM	APL-2 Monthly
AEOM	APL-2 Every-Other-Month
AESI	Adverse Event of Special Interest
AMD	Age-related Macular Degeneration
ANCOVA	Analysis of Covariance
ATC	Anatomic Therapeutic Chemical
AUC	Area Under the Curve
BCVA	Best-Corrected Visual Acuity
BLQ	Below Limit of Quantification
CNS	Clinical Network Services Pty Ltd
CNV	Choroidal Neovascularization
CRC	Central Reader Centre
CSR	Clinical Study Report
CV	Coefficient of Variation
eCRF	Electronic Case Record Form
EOM	Every Other Month
FFA	Fundus Fluorescein Angiograms
FAF	Fundus Autoflourescence Photographs
GA	Geographic Atrophy
ITT	Intent To Treat
IOP	Intra Ocular Pressure
IR	Infrared Reflectance
IV	Intravenous
IVT	Intravitreal
IWRS	Interactive Web Response System

Abbreviation	Description
LL-BCVA	Low Luminance Best-Corrected Visual Acuity
LLOQ	Lower Limit of Quantification
LL-VA	Low Luminance Visual Acuity
logMAR	$\log_{10}$ of the Minimal Angle of Resolution
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent To Treat
MMRM	Mixed effects Model for Repeated Measures
MNV	Macular Neovascularization
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per protocol
PT	Preferred Term
REML	Restricted Maximum Likelihood
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SEOM	Sham Every-Other-Month
SM	Sham Monthly
SMC	Safety Monitoring Committee
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TLFs	Tables, Listings, Figures
WHO	World Health Organization

2. INTRODUCTION

This statistical analysis plan (SAP) for study POT-CP121614 is developed based on the final protocol version 3.0 and CRF version (20th January 2016). The purpose of this SAP is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are comprehensive and appropriate for the analysis of study objectives specified in the protocol. Any amendments to the SAP will be made prior to database lock. Any additional analyses not described in the final SAP or deviations from the final SAP will be documented in the clinical study report (CSR).

This SAP supersedes the protocol in all specifications associated with data analyses and statistical methodologies.

Study POT-CP121614 has a 12-month treatment period with an additional 6-month follow-up period. The main database lock for the study will occur when all subjects complete the Month 12 visit or have withdrawn earlier from the study and the data have been collected and cleaned. The CSR will summarize data up to 12 months. All post Month 12 follow-up data collected prior to the database lock may be presented on key safety outcomes. When all subjects complete the study (i.e. the final follow-up visit at Month 18) or have withdrawn earlier from the study and all data are collected and cleaned, the final database lock will occur. An addendum to the CSR will be developed to summarize the additional follow-up data. For key endpoints, the summary will include data for the overall study period (treatment + follow-up).

2.1. RESPONSIBILITIES

All genotyping analyses will be performed and reported by The Institute of Human Genetics at the University of Regensburg. Clinical Network Services Pty Ltd (CNS) will perform the statistical analyses of all other endpoints and are responsible for the production and quality control of tables, figures and listings (TLFs) for these endpoints.

3. STUDY OVERVIEW

3.1. 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 (GA) associated with Age-related Macular Degeneration (AMD).

3.2. 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 AMD.

Subjects diagnosed with GA associated with AMD in the study eye and who meet all inclusion/exclusion criteria will be included in the study. The study will randomize approximately 240 subjects across 40 multinational sites to obtain at least 200 subjects who complete the study.

Subjects should be screened 14 (±5) days before receiving APL-2. Subjects who meet all inclusion and exclusion criteria and are confirmed as eligible by the Central Reader Centre (CRC) will return to the clinic for the randomization visit (Day 1). 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 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.

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.

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 (AESI outlined in Protocol Section 10.1.3). Additional regular or ad-hoc safety reviews will be scheduled as recommended by the SMC.

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).

3.3. DETERMINATION OF SAMPLE SIZE

With a total sample size of 201 evaluable subjects there is approximately 90% power to claim a statistically significant difference in means among treatment groups if there is a ‘true’ 30% reduction in annual increase of square root GA area for the APL-2 treated groups compared with the pooled sham treatment group. This assumes that, in the absence of treatment, average square root area change is 0.33mm/year[1,2], the standard deviation of annual square root area change is

0.2mm/year and a 2-sided test at the 10% level of significance.

Assuming a 15-20% loss to follow-up, a total sample size of 240 subjects (AM=80, AEOM=80, SM=40 and SEOM=40) will be required to obtain 201 evaluable subjects (i.e. subjects who complete the study).

3.4. TREATMENT ASSIGNMENT AND BLINDING

Each subject will be assigned a unique screening number upon entering screening. Subjects who complete the study screening assessments and meet all eligibility criteria will be scheduled to enter the study and be randomized. The randomization of subjects will be done via a web-based randomization system (IWRS) which will assign a unique randomization number. Subjects will be randomized in a 2:2:1:1 ratio to receive APL-2 monthly (AM), APL-2 every-other-month (AEOM), sham injection monthly (SM) or sham injection every-other-month (SEOM), respectively. The randomization will be stratified by site.

The study is single-masked. Subjects and assessors of efficacy assessments (imaging or visual acuity) are masked to treatment (APL-2 or sham injection). The investigators, site personnel not performing efficacy assessments, vendors, sponsor and CRO personnel will be unmasked to treatment assignment. Additionally the CRC, who will perform the independent review of efficacy evaluation images, will be masked to provide an objective assessment of these evaluations.

The independent SMC will be provided unmasked safety data for their safety assessment.

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 endeavour to notify the Sponsor prior to unmasking a subject.

3.5. ADMINISTRATION OF STUDY MEDICATION

Subjects will receive either 15mg APL-2/100 µL IVT injections or sham injections. Injections will either be monthly or EOM depending on the treatment group. The number of injections for each treatment group is:

Table 1: Number of Injections

Treatment Arm	Number of Injections
APL-2 Monthly for 12 months	13
APL-2 EOM for 12 months	7
Sham Monthly for 12 months	13
Sham EOM for 12 months	7

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

To minimize intra ocular pressure (IOP) elevation after IVT injection of APL-2, decompression of the eye must be performed before all APL-2 (or sham) injections. This is done by applying moderate pressure to the globe with cotton swabs for 30-60 seconds during anaesthetic preparation.

3.6. STUDY FLOWCHART

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

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.

Note: The study schedule refers to the first day of dosing as Day 0 (Visit 2). For reporting purposes CDISC standards will be used and therefore it is necessary to refer to the first day of dosing as Day 1. Consequently, throughout the SAP text Day 1 is referred to as the first day of dosing, however the study schedule table is taken directly from the protocol and has not been changed.

4. ENDPOINTS

4.1. PRIMARY EFFICACY ENDPOINT

The primary endpoint is the annual growth rate of GA area in the study eye as measured by the mean change in square root area of GA lesion from baseline to Month 12 based on the Fundus Autoflourescence Photographs (FAF). Baseline will be taken as the last available non-missing assessment prior to first study drug administration, this should be the screening assessment for the primary endpoint.

A secondary endpoint will investigate the untransformed value collected i.e. mean change in area of GA lesion from baseline to Month 12 based on the FAF.

Upon reviewing the 12-month results, different growth rates in the GA lesion were observed across visit to visit. Therefore, the change in GA lesion from Month 6 to Months 12 and 18, and the change from Month 12 to Month 18 will be evaluated as exploratory endpoints. The analyses will be performed for both square root transformed and untransformed measurements of the GA lesion.

4.2. SECONDARY AND EXPLORATORY EFFICACY ENDPOINTS

4.2.1. Best-Corrected Visual Acuity (BCVA)

BCVA is performed following refraction by a certified VA examiner and is done prior to any examination requiring administration of eye drops to dilate the eye or any examination requiring contact with the eye. Larger values indicate better visual acuity. BCVA is the sum of $BCVA_1$ (correct identifications at 1 meter) and $BCVA_4$ (correct identifications at 4 meters). If $BCVA_1$ is not collected because visual acuity has been identified as 20/200 or better at the 4-meter test, then a value of 30 will be used in the calculation of BCVA.

The endpoint is change from baseline in BCVA. Baseline will be taken as the last available non-missing assessment prior to first study drug administration. The change from baseline will also be categorized as follows:

- ≥15 letters improvement from baseline
- ≥10 letters and <15 letters improvement from baseline
- ≥5 letters and <10 letters improvement from baseline
- Minimal change from baseline; defined as -4 to 4 letters
- ≥5 letters and <10 letters worsening from baseline
- ≥10 letters and <15 letters worsening from baseline
- ≥15 letters worsening from baseline

The Snellen equivalent value is also collected as part of the BCVA assessment. The Snellen equivalent categorical response at each visit will be investigated. In addition, the Snellen value will

be transformed to $\log_{10}$ of the reciprocal of the Snellen value, this is more commonly known as $\log_{10}$ of the minimal angle of resolution value (logMAR). The converted logMAR scores will be rounded to one decimal. For a Snellen value of 20/20 logMAR is 0 and as vision worsens logMAR increases and as vision improves logMAR decreases. A change of 0.1 on the logMAR scale represents a change of 1 line. The change from baseline in logMAR will be investigated.

4.2.2. Macular Neovascularization (MNV)

The incidence of MNV in the study eye will be investigated. A clinical review of all ocular adverse events will be performed prior to database lock to identify all cases of MNV.

4.2.3. Low Luminance Best-Corrected Visual Acuity (LL-BCVA)

LL-BCVA is performed by a certified VA examiner and is done prior to any examination requiring administration of eye drops to dilate the eye or any examination requiring contact with the eye. Larger values indicate better visual acuity. LL-BCVA is the sum of LL-$BCVA_1$ (correct identifications at 1 meter) and LL-$BCVA_4$ (correct identifications at 4 meters). If LL-$BCVA_1$ is not collected because the low luminance visual acuity has been identified as 20/200 or better at the 4-meter test, then a value of 30 will be used in the calculation of LL-BCVA.

The endpoint is change from baseline in LL-BCVA. Baseline will be taken as the last available non-missing assessment prior to first study drug administration. The change from baseline will also be categorized as follows:

- ≥15 letters improvement from baseline
- ≥10 letters and <15 letters improvement from baseline
- ≥5 letters and <10 letters improvement from baseline
- Minimal change from baseline; defined as -4 to 4 letters
- ≥5 letters and <10 letters worsening from baseline
- ≥10 letters and <15 letters worsening from baseline
- ≥15 letters worsening from baseline

The Snellen equivalent value is also collected as part of the LL-BCVA assessment. The Snellen equivalent categorical response at each visit will be investigated. In addition, the Snellen value will be transformed to logMAR (as described in Section 4.2.1). The change from baseline in logMAR will be investigated.

4.2.4. Low Luminance Visual Acuity (LL-VA) Deficit

The LL-VA deficit is calculated as BCVA minus LL-BCVA. The endpoint of interest is change from baseline in LL-VA deficit. Baseline will be taken as the last available non-missing assessment prior to first study drug administration. Baseline LL-VA deficit should be derived from BCVA and LL-BCVA

at the same time point for each subject; otherwise baseline LL-VA deficit will be set to missing.

4.2.5. Foveal Encroachment (Distance of GA Lesion from Fovea)

Foveal encroachment over time in the study eye, as measured by FAF, will be assessed by change from baseline in distance of GA lesion from fovea. Baseline will be taken as the last available non-missing assessment prior to first study drug administration.

4.2.6. Drusen Size

Drusen is assessed in both eyes by color photography at screening and end of study or early termination. Baseline will be taken as the last available non-missing assessment prior to first study drug administration. The endpoints are:

- Study eye drusen size (none, small, intermediate or large). The maximum size recorded will be used. So for example if both intermediate and large drusen are recorded then the size will be large. The size will be assigned as small if there are drusen present but none are intermediate or large.
- The number of intermediate or large drusen recorded in the study eye (0-5, 6-10, 11-20 or >20).

4.2.7. GA Lesion Size Measured by SD-OCT

In this study, Spectral Domain Optical Coherence Tomography (SD-OCT) is measured by one of two machines (Ziess Cirrus or Heidelberg Spectralis). The same machine is used for a subject throughout the study. *Note: approximately 80% of subjects have been assessed using the Spectralis machine.*

Depending on data availability, GA lesion size per SD-OCT will be investigated for those subjects who have SD-OCT assessed with the Cirrus machine. The endpoint is change from baseline in square root area for GA lesion in the study eye as measured by SD-OCT. Baseline will be taken as the last available non-missing assessment prior to first study drug administration.

4.2.8. Genetic Polymorphisms

Genetic marker analysis will be performed on blood samples collected at Month 2 for all subjects at selected sites where genetic testing is allowed. The prioritized genes, C3, CFI, CFH, CFB, C2, ARMS2/HTRA1, will be explored to assess whether they are prognostic/predictive factors of the growth in GA area and the APL-2 treatment. For the prioritized genes the following SNPs, that have been highly associated with AMD, will be investigated:

- CFH: rs1061170, rs1410996, rs10737680, rs1048663
- CFB: rs438999, rs541862, rs4151667, rs641153
- C2: rs9332739

- C2/CFB: rs429608
- CFI: rs17440077, rs4698775, rs10033900
- ARMS2/HTRA1: rs10490924
- C3: rs2230199

Additional genes that are not part of the current scope of work may be analysed and summarized in a separate genetic report.

4.3. SAFETY ENDPOINTS

4.3.1. Adverse Events

The primary safety endpoints for the study are the number and severity of treatment emergent adverse events (TEAEs) and adverse events of special interest (AESI). AESI will be identified on the eCRF at the time of reporting and include:

- 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 (or Sham) 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 (wet) AMD in the study eye or fellow eye requiring surgical intervention (Note: Intravitreal administration of anti-VEGF agents are not considered surgical interventions.)

A clinical review of all ocular AEs will be performed prior to database lock to ensure all AESI have been identified.

4.3.2. Intraocular pressure (IOP)

Intraocular pressure (IOP) will be measured using either Tonopen, iCare or Goldmann applanation tonometer. The same method will be used for all measurements in the same subject throughout the study. IOP is collected for the study eye pre and post injection at each study visit.

A safety endpoint for IOP is change from baseline in study eye IOP over time. Baseline will be taken as the last available non-missing assessment prior to first study drug administration.

The acute change in IOP after each injection (i.e., change from pre-injection to post-injection value) will also be analysed as another endpoint for IOP. Missing pre-injection IOP values will be imputed

with the last available pre-injection IOP value at previous visits. Missing post-injection values will not be imputed.

Values ≥30 mmHg will also be identified. Missing IOP values will not be imputed for this indicator endpoint.

4.3.3. Anterior Segment Examination

The anterior segment examination data is collected on the slit lamp examination eCRF page. The anterior segment examination is performed throughout the study for the study eye and at screening and end of study only for the fellow eye. The following endpoints will be investigated for the study eye and fellow eye (screening and end of study only):

- Abnormal reaction to light
- Active inflammation present in cornea
- Abnormal anterior chamber
- Any opacity in lens. Note if response to lens question is missing but anterior chamber response is normal then response will be defined as no opacity in the lens.
- Aqueous reaction - flare (0, trace, 1+, 2-3+, 4+). Note if response to aqueous reaction flare question is missing but anterior chamber response is normal then response will be defined as 0.
- Aqueous reaction - cells (0, trace, 1+, 2+, 3+, 4+). Note if response to aqueous reaction cells question is missing but anterior chamber response is normal then response will be defined as 0.

4.3.4. Posterior Segment Examination

The posterior segment examination data is collected on the dilated binocular indirect ophthalmoscopy eCRF page. The posterior segment examination is performed throughout the study for the study eye and at screening and end of study only for the fellow eye. The following endpoints will be investigated for the study eye and fellow eye (screening and end of study only):

- Posterior segment abnormalities (none, mild, moderate, severe)
- Presence of posterior vitreous detachment
- Presence of retinal haemorrhage/detachment
- Vitreal haemorrhage density (none, 1+, 2+, 3+, 4+)
- Vitreous cells evaluation (none, 1+, 2+, 3+, 4+)

4.3.5. LOCS III Lens

If an abnormal lens finding is noted during the anterior segment (slit lamp) examination, at any visit, then the finding should be further characterized with LOCS III. All subsequent visits for that subject will include LOCS III. LOCS III is used to grade the severity of age-related cataracts. LOCS III

grading will not be assessed for pseudophakic and aphakic subjects as they do not have opacity.

For the subset of subjects having this additional ophthalmology assessment, the endpoints are:

- [NO] nuclear opalescence (range 0.1 to 6.9)
- [NC] nuclear color (range 0.1 to 6.9)
- [C] cortical cataract (range 0.1 to 5.9)
- [P] posterior subscapular cataract (range 0.1 to 5.9)

For all endpoints a value of 0.1 represents a completely clear or colourless lens. Baseline will be taken as the last available non-missing assessment prior to first study drug administration. For subjects who do not have a baseline measurement for LOCS III but have a baseline anterior segment assessment which confirms no opacity in the lens, then it will be assumed that there were no abnormal lens findings at baseline and a value of 0.1 will be assigned to each of the endpoints. If the baseline anterior segment assessment does not confirm opacity of the lens or is missing then the baseline for the LOCS III endpoints will be taken as missing.

The change from baseline in each of the endpoints will be assessed.

4.3.6. Other Safety Endpoints

Safety will also be assessed through vital signs, laboratory safety data and antigenicity data. Changes from baseline will be calculated taking baseline as the last measurement prior to the first injection.

4.4. PHARMACOKINETIC ENDPOINTS

Plasma APL-2 concentrations will be determined from multiple samples taken during the course of the study - screening, and at each visit from Day 7 to termination (Day 540).

C_{max} should occur at Day 7 ($C_{Day\ 7}$).

4.5. PHARMACODYNAMIC ENDPOINTS

The pharmacodynamic (PD) endpoints include changes from baseline and percentage changes from baseline for the complement parameters CH50 and C3. Baseline will be taken as the last available non-missing assessment prior to first study drug administration.

5. ANALYSIS SETS

5.1. SCREENED POPULATION

The screened population will include all subjects who signed the informed consent form and are screened for participation in this study. This population will only be used for the purposes of

describing the subject disposition and for listing the data.

5.2. RANDOMIZED POPULATION

The randomised population will include all randomized subjects. This population will only be used for the purposes of describing the subject disposition.

5.3. SAFETY POPULATION

The safety population will include all subjects randomized who receive at least one injection of study medication. The safety population summary groups will be based on the actual treatment received for the whole duration of the study. The grouping rule for subjects who receive study medication from the incorrect injection during the study will be decided on a case by case basis before database lock. This population will be used for all safety analyses.

5.4. INTENT TO TREAT (ITT) POPULATION

The ITT population will include all subjects randomized who receive at least one injection of study medication. Subjects will be included in their randomized treatment group even if they receive the wrong study medication.

5.5. MODIFIED INTENT TO TREAT (MITT) POPULATION

The MITT population will include all subjects randomized who receive at least one injection of study medication and have at least one visit at or after Month 2 where primary efficacy data is collected. Month 2 is the first visit on-treatment where lesion area is measured. Subjects will be included in their randomized treatment group even if they receive the wrong study medication. This population will be used for the primary efficacy analysis and other analyses for efficacy and exploratory endpoints.

If the MITT and the ITT do not differ then only the ITT will be used. If there are minimal differences between these 2 populations then a decision will be made prior to database lock on whether to only use one of these populations for reporting.

5.6. PER PROTOCOL (PP) POPULATION

The PP population will include all subjects in the MITT population who have not violated any inclusion or exclusion criteria and/or deviated from the protocol, in a way that could influence their efficacy assessment. Subjects will be excluded if they:

- Received less than 75% of their expected injections prior to Month 12. For subjects receiving monthly injections this will be less than 9 injections and for subjects receiving injections EOM this will be less than 4 injections.

- Receive the incorrect study medication throughout the study

Subjects will be included in their 'as treated' treatment group. Note that this will be the same as the randomized treatment because receiving the wrong study medication is a major deviation.

Data listings, including protocol deviations (Section 5.9), will be provided to identify subjects to be excluded from the PP population prior to database lock. Precise reasons for excluding subjects will be documented prior to locking the database.

5.7. PHARMACOKINETIC (PK) POPULATION

The PK population will include all subjects in the safety population who have at least one quantifiable concentration of APL-2 (even if <LLOQ).

5.8. PHARMACODYNAMIC (PD) POPULATION

The PD population will include all subjects in the safety population who have at least one quantifiable post dose PD parameter.

5.9. PROTOCOL DEVIATIONS

All protocol deviations will be reviewed and documented before database lock. Protocol deviations will be recorded by the site staff, study monitors and medical monitor reviewers. They may also be identified through programmable checks of the data.

Key protocol deviations include:

- Violations of inclusion and exclusion criteria. This includes unknown violations at enrolment and on-study violations, like taking a prohibited medication
- Receive the incorrect study medication

Protocol deviations will be categorized as either major or minor prior to database lock. All protocol deviations will be listed.

5.10. DATA REVIEW FOR ANALYSIS POPULATIONS

After all the data has been entered and verified in the database, a review will be performed to define the analysis populations. The review will also check the quality of the data, identify outliers and make decisions on how to deal with problems in any data (e.g. missing values, withdrawals, protocol deviations). After the pre-analysis review, resolution of all issues and documentation of all decisions the database will be locked.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

All statistical tests will be 2-sided at the 0.1 level of significance. To understand the clinical significance of the estimated treatment effects and to aid interpretation of the formal hypothesis testing 2-sided 95% CI will also be provided. There will not be any adjustments for multiple comparisons.

For all independent ophthalmic assessments (performed by DARC laboratory), if assessments by only two independent readers are available, then the mean of the 2 readings will be used in the calculation of summary statistics. If assessments by three independent readers are available, then the median of the three readings will be used for the summary calculations.

Continuous variables will be summarized using the number of non-missing observations (n), mean, standard deviation (SD), median, minimum, and maximum. Geometric mean and coefficient of variation (CV) will be included for PK parameters, where appropriate. Categorical variables will be summarized using frequencies and percentages. Unless stated otherwise, for all percentages, the number of subjects in the analysis population for the treatment group will be the denominator.

Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more decimal place than the original values, and standard deviations should be printed out to 2 more decimal places than the original values. The minimum and maximum should report the same number of decimal places as the original values. Percentages will be displayed with 1 decimal place; except percentages will not be presented when the count is zero and 100% will be presented as an integer.

Unless stated otherwise, baseline will be taken as the last available non-missing assessment prior to first study drug administration.

Subjects can discontinue treatment but remain in the study for follow-up. All assessments will be included in summary tables or analyses unless stated otherwise.

For all summary tables, data will be presented by treatment group and by pooled sham and pooled APL-2. For summaries by-visit pooled sham and pooled APL-2 will only be presented for the bi-monthly visits. The treatment group labels for summary tables will be:

- APL-2 Monthly
- APL-2 EOM
- APL-2 Pooled
- Sham Monthly
- Sham EOM
- Sham Pooled

In general, all summary tables will display the treatment groups in the above order except for cases where it's more convenient for comparison purposes to layout the Sham Pooled group with both AMP-2 Monthly and APL2- EOM groups on the same page. In by-visit summary tables the baseline will be summarized using all available data, but also for each visit using only the baseline data from subjects with available data at the visit.

All data will be listed. Data listings will be presented by treatment group. Data listings will present study days in addition to dates, where study day is derived as (assessment date – first day of dosing) +1. The first day of dosing will be identified as Study Day 1. The analysis visit (derived from visit windowing – refer to Section 6.3) alongside the actual visit and the time since last dose will also be included in relevant listings.

All statistical analyses will be performed using SAS® (Version 9.4 or higher, SAS Institute Inc., Cary, NC, USA).

6.2. MISSING DATA

All possible efforts will be made to minimize missing data. As missing data may potentially bias the outcome of the statistical analyses and the subsequent estimation of the magnitude of the treatment effect, different strategies will be applied to provide a balanced assessment of treatment efficacy.

Where specified screen values or pre-dose unscheduled measurements may be used as a baseline value in the event of missing Day 1 measurements.

Handling of missing dates/times for the start/stop of medications and adverse events are detailed in Sections 7.5 and 11.1 respectively.

The original data will always be presented in the listings.

6.2.1. Efficacy Data

Missing data may result from a subject discontinuing, a particular assessment missed at a visit or a complete visit missed. For the primary analysis sensitivity analyses will be conducted to assess the influence of missing data. These include:

- Last observation carried forward (LOCF). The LOCF approach will replace missing Month 12 (or Month 18) data with the last observation recorded.

- Linear mixed effects model for repeated measures (MMRM). The MMRM approach assumes data are missing at random and uses a restricted maximum likelihood (REML) repeated measures model to analyse available data.

6.2.2. Pharmacokinetic and Pharmacodynamic Data

APL-2 concentrations reported as below the limit of quantification (BLQ) will be taken as zero for linear plots, and equal to the lower limit of quantification (LLOQ) for semi-logarithmic plots. For the computation of descriptive statistics, BLQ will be taken as zero, except for the calculation of the geometric mean where the LLOQ will be used.

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

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

6.3. VISIT WINDOWS

Analysis visits will be derived with windowing for the Day 7 and monthly visits. Screening can be up to 2 weeks before start of study treatment. Baseline is defined as the date of randomization. Table 2 below defines the analysis windows for the visits. If 2 or more treatment visits occur within a window, the closest visit to the target day will be used as that analysis visit; if 2 visits are equidistant from the scheduled analysis visit day, the later analysis visit will be used.

Visit windowing will be reviewed prior to reporting and assessments where the actual study day does not fall within the protocol visit window for the Day 7 or monthly visits will be identified and the allocation reviewed. For the two EOM treatment groups, visits that lie within the window for an odd month will not be summarized.

Table 2: Analysis Windows

Analysis Visit	Target Study Day	Protocol Visit Window (days)	Analysis Window (days)
Screening	-14	± 5	NA
Baseline	1	0	NA
Day 7	8	± 2	2 to 16
Month 1	31	± 6	17 to 46
Month 2	61	± 6	47 to 76
Month 3	91	± 6	77 to 106
Month 4	121	± 6	107 to 136
Month 5	151	± 6	137 to 166
Month 6	181	± 6	167 to 196
Month 7	211	± 6	197 to 226
Month 8	241	± 6	227 to 256
Month 9	271	± 6	257 to 286

Analysis Visit	Target Study Day	Protocol Visit Window (days)	Analysis Window (days)
Month 10	301	± 6	287 to 316
Month 11	331	± 6	317 to 346
Month 12	361	± 6	347 to 376
Month 15	451	± 14	412 to 481
Month 18	541	± 14	511 to 571
EOS	541	± 14	Final Assessment

EOS = End of Study

6.4. SUBGROUPS

The following subgroups will be considered:

- Country: Australia, New Zealand and United States
- Reticular pseudodrusen at baseline: present, absent
- Age group: split into 3 similar sized groups (<75 years, 75-<85 years, ≥85 years)
- LL-VA deficit at baseline: < overall median value, ≥ overall median value
- Fellow-eye CNV at baseline: yes, no
- GA presence at baseline: unilateral, bilateral
- GA lesion size in the study eye: < 10 mm^2, ≥ 10 mm^2
- Sex: male, female

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. PATIENT DISPOSITION AND WITHDRAWALS

For the screened population the number of subjects screened, the number who failed screening and the reason for screen failure will be presented. For the ITT population the following will be presented by treatment group and overall:

- Number of subjects randomized
- Number of subjects completed treatment
- Number of subjects withdrawn from treatment and reason for withdrawal
- Number of subjects completed study
- Number of subjects withdrawn from study and reason for withdrawal
- Number of subjects in each analysis population and reason for exclusion from the PP population

The number of subjects randomized, completed treatment, withdrawn from treatment, completed study and withdrawn from study at each site will also be summarized.

A summary of disposition by visit and by treatment group and overall will also be presented for the ITT and MITT populations. This disposition will be split by those receiving treatment (i.e. ongoing in study at the time of the visit) and those discontinued treatment prior to visit, and will include the following:

- Number of subjects ongoing in study at time of visit
  - Number of subjects attended visit
  - Number of subjects receiving injection
  - Number of subjects discontinued treatment prior to visit
  - Number of subjects missed visit
- Number of subjects discontinued study prior to visit

7.2. DEMOGRAPHIC CHARACTERISTICS

Demography (gender, race, ethnicity, age [years], country) will be summarized for the ITT and MITT populations by treatment group and overall. Age will be summarized using summary statistics for continuous variables. Categorical age (<65 years, 65-<75 years, 75-<85 years and ≥85 years), gender, race, ethnicity and country will be summarized using summary statistics for categorical variables.

Age = (informed consent date - date of birth + 1)/365.25 truncated to complete years.

7.3. BASELINE CHARACTERISTICS

Baseline characteristics (GA lesion size (FAF), BCVA, LL-BCVA, drusen size, IOP, LL-VA deficit, GA presence in the fellow eye, presence of reticular pseudodrusen, fellow eye CNV presence and study eye) will be summarized for the ITT and MITT populations by treatment group and overall. GA lesion size, BCVA, LL-BCVA, drusen size, IOP, LL-VA deficit and presence of reticular pseudodrusen will be summarized separately for the study eye and the fellow eye. GA lesion size (measured by FAF), BCVA, LL-BCVA and study eye IOP will be summarized using summary statistics for continuous variables. Drusen size (none, small, intermediate or large), LL-VA deficit (< overall median value, ≥ overall median value), GA presence in the fellow eye (yes, no), presence of reticular pseudodrusen, fellow eye CNV presence and study eye (OD, OS) will be summarized using summary statistics for categorical variables.

7.4. MEDICAL HISTORY AND CONCOMITANT DISEASES

Medical history will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) Version available. Summaries will be presented for the ITT and MITT populations by System Organ Class (SOC) and Preferred Term (PT) with counts and percentages by treatment group and overall. Each subject will be counted only once in each SOC or SOC/PT summary.

All ocular history, will be summarized for the ITT and MITT populations by System Organ Class (SOC)

and Preferred Term (PT) with counts and percentages by treatment group and overall. The summaries will be produced separately for the study eye and the fellow eye. Any ocular condition associated with both eyes will be included in both summaries.

7.5. PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be coded using the latest WHO Drug Dictionary version available. Medication will be presented for the safety population by ATC level 2 (therapeutic main group) and ATC level 5 (standardized medication name) with counts and percentages by treatment group and overall. A subject who took more than one medication will be counted only once if these medications belong to the same extended ATC classification. In addition, prior and concomitant medications used in study eye will be summarized. Similar summaries will be provided for the medications used in the fellow eye.

Prior medications will be defined as those medications started prior to the administration of study drug on Day 1. Concomitant medications will be defined as those medications taken following the first administration of study drug on Day 1. Hence medications started before study dosing, but continuing after are considered as both prior and concomitant medications. The listing of medications will identify prior and concomitant medications.

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

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

7.6. EXTENT OF EXPOSURE

The number of injections, number of missed injections and duration of treatment will be summarized by treatment group for the ITT and MITT populations using frequency counts and percentages. The number of subjects receiving injections at each of the Months (1-12) will also be summarized by treatment group using frequency counts and percentages. As treatment is administered in the clinic there is no need to assess compliance.

Duration of treatment (days) = date of last injection – date of first injection +1

The number of missed injections is defined as the scheduled injections missed up to discontinuation of study treatment.

Study drug administration will be listed by treatment group. In addition, a listing of total number of injections, duration of treatment, date and day of first and last dose and number of missed injections will be provided.

8. EFFICACY

For the primary 12-month analyses, all efficacy data up to Month 12 will be included. For the final 18-month database lock, all by-visit summaries and analyses of change from baseline over time that are specified in this section, whenever applicable, will be repeated to include all data up to Month 18. The summary or analysis of data at Month 12 will be repeated for the data at Month 18.

8.1. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

The primary endpoint is the change from baseline in square root area for GA lesion at Month 12 as measured by FAF. Baseline will be taken as the last available non-missing assessment prior to first study drug administration, this should be the screening assessment for the primary endpoint.

The change from baseline in square root area for GA lesion at Month 2, 6 and 12 will be analysed for the MITT population with a MMRM. The model will include the fixed effects of treatment (3 groups: AM, AEOM and Sham), baseline square root area for GA lesion, visit (2, 6 and 12 months), treatment by visit interaction, visit by baseline interaction and treatment by baseline interaction. An unstructured covariance structure will be used to model the within subject error. The Kenward-Rogers approximation will be used to estimate the denominator degrees of freedom. If the treatment by baseline interaction is not significant at the 10% level then this term will be removed from the model. If significant at the 10% level results will be presented both including and excluding this term and the nature of the interaction will be investigated before deciding on an approach for presenting results that include the treatment by baseline interaction.

All available data will be included in the analysis. The analysis model table will be presented. The treatment comparisons (AM vs Sham, AEOM vs Sham and AM vs AEOM) at Months 2, 6 and 12 will also be presented with the estimate, standard error and 95% CI. If the treatment effect is significant at the 10% level then the treatment means will be compared using the least significant difference (LSD) method and the p-value presented. In addition, the estimated mean (i.e. Least-Squares mean) change from baseline in square root area for GA lesion with ± SE of mean change, will be plotted over time by treatment group.

The model assumptions will be checked by evaluating the model residuals. A Shapiro-Wilks test will

be performed on the residuals; a p-value > 0.1 will be considered proof of normality. If a Shapiro-Wilks p-value is ≤ 0.1, the residual plots will be evaluated for symmetry. If the evaluation of residuals indicates a problem with the model assumptions, another transformation of the data will be considered.

The change from baseline in square root area for GA lesion will be summarized by treatment group and visit for the MITT population using the observed data and replacing missing values with predicted values from the model. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data. The absolute values for missing data will be derived as the predicted change from baseline in square root area for GA lesion plus observed baseline value.

The observed values for the square root area for GA lesion will be summarized by treatment group and visit for the MITT population. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data. The observed mean change from baseline in square root area for GA lesion with ± SE of mean change, will be plotted over time by treatment group.

8.1.1. Sensitivity Analyses of the Primary Endpoint

The robustness of the primary analysis will be evaluated by repeating the primary analysis with the per-protocol population.

In addition, the following sensitivity analyses will be conducted using the MITT population:

- A MMRM analysis including only data which is within a specific time period of the last injection. Month 6 data will be included if a subject was dosed on or after Month 4, and Month 12 will be included if a subject was dosed on or after Month 8. All Month 2 data will be included, as the criteria to be included in the MITT population requires a subject to have had at least one dose of study medication. The primary analysis will be repeated using this subset of data.
- An analysis using an LOCF method for handling missing data as specified in Section 6.2.1. All available Month 12 data will be included and missing data will be replaced using LOCF method. An analysis of Covariance (ANCOVA) model will be fitted for the Month 12 change from baseline in square root area for GA lesion, that includes baseline as a covariate and treatment (3 groups: AM, AEOM and Sham).
- Completer analysis i.e. observed data for those subjects who complete the treatment period (for subjects receiving monthly injections this will be 12 injections and for subjects receiving EOM injections this will be 6 injections) and have their Month 12 assessment. The analysis model will be the same as for the primary analysis.

For each approach, a summary over time will be presented. The analysis model table will be presented. The treatment comparisons (AM vs Sham, AEOM vs Sham and AM vs AEOM) will also be presented with the estimate, standard error and 95% CI. If the treatment effect is significant at

the 10% level then the treatment means will be compared using the least significant difference (LSD) method and the p-value presented.

8.1.2. Additional Analyses of the Primary Endpoint

The completer cases at Month 6 i.e. observed data for those subjects who complete 6 months of treatment (for subjects receiving monthly injections this will be 6 injections and for subjects receiving EOM injections this will be 3 injections) and have their Month 6 assessment; will be analysed using the same model as the primary analysis. This analysis will be repeated for the completer cases at Month 18 i.e. subjects who complete the treatment period (for subjects receiving monthly injections this will be 13 injections and for subjects receiving EOM injections this will be 7 injections) and have their Month 18 assessment.

The untransformed change from baseline in area for GA lesion at Month 2, 6 and 12 will be analysed for the MITT population using the same model as the primary analysis. The estimated mean change from baseline in area for GA lesion with ± SE of mean change, will also be plotted over time by treatment group.

Additional summaries and analyses will be performed for the subgroups detailed in Section 6.4. These analyses will be based on the MITT population and will use the same analysis approach as specified in Section 8.1, however the treatment by baseline interaction will only be investigated if it is significant for the primary analysis.

In addition, the observed mean change from baseline in square root area for GA lesion ± SE of mean change, will be plotted over time by treatment group and reticular pseudodrusen at baseline (present/absent) on the same plot.

8.1.3. GA Lesion Growth Rate between Timepoints of Interest

Upon reviewing the 12-month data of the study for the primary analysis, a different growth rate was observed from Month 6 to Month 12 as compared from Baseline to Month 6 for the active group. To assess the growth rate between any two timepoints of interest (Months 6, 12 and 18), the change in GA lesion from Month 6 to Month 12, Month 12 to Month 18, and Month 6 toMonth 18 will be summarized. One-way ANOVA will be used to compare the treatment effect on the GA lesion growth between the given timepoints. The pairwise treatment group comparisons will be done based on the least significant different (LSD) t-test to adjust the multiplicity.

8.2. SECONDARY AND EXPLORATORY EFFICACY ENDPOINTS AND ANALYSIS

8.2.1. Best-Corrected Visual Acuity (BCVA)

The change from baseline in BCVA score over time to Month 12 will be analysed in the same way as the primary endpoint for the MITT population. The model will include the fixed effects of treatment (3 groups: AM, AEOM and Sham), baseline BCVA score, visit (Day 7, Months 2, 4, 6, 8, 10 and 12), treatment by visit interaction, visit by baseline interaction and treatment by baseline interaction. An unstructured covariance structure will be used to model the within subject error. The Kenward-Rogers approximation will be used to estimate the denominator degrees of freedom. If the treatment by baseline interaction is not significant at the 10% level then this term will be removed from the model. If significant at the 10% level results will be presented both including and excluding this term and the nature of the interaction will be investigated before deciding on an approach for presenting results including the treatment by baseline interaction.

The analysis model table will be presented. The treatment comparisons (AM vs Sham, AEOM vs Sham and AM vs AEOM) at Months 6 and 12 will also be presented with the estimate, standard error and 95% CI. If the treatment effect is significant at the 10% level then the treatment means will be compared using the least significant difference (LSD) method and the p-value presented.

The change from baseline in BCVA score will be summarized by treatment group and visit for the MITT population using the observed data. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data.

The estimated mean change from baseline in BCVA score ± SE of mean change, will be plotted over time by treatment group. The plot will be repeated for the observed mean change from baseline in BCVA score ± SE of mean change.

The categorical changes (improvements of ≥5 to <10, ≥10 to <15 and ≥15, minimal/no change, worsening of ≥5 to <10, ≥10 to <15 and ≥15, and missing changes) will be summarized by treatment group and visit for the MITT population.

The Snellen equivalent categorical response will be summarized by treatment group and visit for the MITT population. The observed logMAR changes from baseline will also be summarized by treatment group and visit for the MITT population. The listing of BCVA data will also include the logMAR values.

The relationship between GA lesion size change from baseline as recorded by FAF and changes from baseline in BCVA will also be investigated. A scatter plot of changes from baseline at Month 12 in GA lesion size as measured by FAF versus changes from baseline at Month 12 in BCVA will be presented. Treatment groups will be identified on the plot. The Pearson correlation coefficient for each treatment group will also be presented. Similar summary and figures will be provided for

relationship at Month 18. To assess whether there is a delay in visual acuity decline compared to GA growth, the scatter plot of the changes from baseline for GA lesion at Month 6 vs BCVA at Month 12, and GA lesion at Month 12 vs BCVA at Month 18 will be provided.

8.2.2. Macular Neovascularization (MNV)

The incidence and exposure adjusted incidence of macular neovascularization (MNV) TEAEs in the study eye will be summarized for the MITT population.

Exposure adjusted incidence (or incidence rate per 100-patient-years) = number of subjects experiencing MNV / total subject time at risk (in years) × 100

Total subject time at risk is the time from first study drug administration date to first MNV event date +1 for subjects who experience an event, or time from first study drug administration date to last visit date +1 for subjects who do not experience a MNV event. Total subject time will be presented in years with a year = 360 days for the calculation.

The incidence for the MITT population will be compared between the active treatment groups (APL-2 Monthly or APL-2 EOM) and sham group using a Fisher's exact chi-squared test. The analysis will be repeated by the subgroup fellow eye CNV at baseline.

8.2.3. Low Luminance Best-Corrected Visual Acuity (LL-BCVA)

The change from baseline in LL-BCVA score over time to Month 12 will be analysed in the same way as the BCVA endpoint (Section 8.2.1) for the MITT population.

The analysis model table will be presented. The treatment comparisons (AM vs Sham, AEOM vs Sham and AM vs AEOM) at Months 6 and 12 will also be presented with the estimate, standard error and 95% CI. If the treatment effect is significant at the 10% level then the treatment means will be compared using the least significant difference (LSD) method and the p-value presented.

The change from baseline in LL-BCVA score will be summarized by treatment group and visit for the MITT population using the observe data. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data.

The estimated mean change from baseline in LL-BCVA score with ± SE of mean change, will be plotted over time by treatment group. The plot will be repeated for the observed mean change from baseline in BCVA score ± SE of mean change.

The categorical changes (improvements of ≥5 to <10, ≥10 to <15 and ≥15, minimal change, worsening of ≥5 to <10, ≥10 to <15 and ≥15, and missing changes) will be summarized by treatment group and visit for the MITT population.

The Snellen equivalent categorical response will be summarized by treatment group and visit for

the MITT population. The observed logMAR changes from baseline will also be summarized by treatment group and visit for the MITT population. The listing of LL-BCVA data will also include the logMAR values.

The relationship between GA lesion size change from baseline as recorded by FAF and changes from baseline in LL-BCVA will also be investigated. A scatter plot of changes from baseline at Month 12 in GA lesion size as measured by FAF versus changes from baseline at Month 12 in LL-BCVA score will be presented. Treatment groups will be identified on the plot. The Pearson correlation coefficient for each treatment group will also be presented. Similar summary and figures will be provided for relationship at Month 18. To assess whether there is a delay in LL-BCVA decline compared to GA growth, the scatter plot of the changes from baseline for GA lesion at Month 6 vs LL-BCVA at Month 12, and GA lesion at Month 12 vs LL-BCVA at Month 18 will be provided.

8.2.4. Low Luminance Visual Acuity (LL-VA) Deficit

The change from baseline in LL-VA deficit over time to Month 12 will be analysed in the same way as the BCVA endpoint (Section 8.2.1) for the MITT population.

The analysis model table will be presented. The treatment comparisons (AM vs Sham, AEOM vs Sham and AM vs AEOM) at Months 6 and 12 will also be presented with the estimate, standard error and 95% CI. If the treatment effect is significant at the 10% level then the treatment means will be compared using the least significant difference (LSD) method and the p-value presented.

The change from baseline in LL-VA Deficit will be summarized by treatment group and visit for the MITT population using the observe data. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data.

The estimated mean change from baseline in LL-VA deficit with ± SE of mean change, will be plotted over time by treatment group. The plot will be repeated for the observed mean change from baseline in LL-VA deficit ± SE of mean change.

8.2.5. Foveal Encroachment (Distance of GA Lesion from Fovea)

The change from baseline in distance of GA lesion from fovea over time to Month 12 will be analysed in the same way as the primary endpoint (Section 8.1) for the MITT population.

The analysis model table will be presented. The treatment comparisons (AM vs Sham, AEOM vs Sham and AM vs AEOM) at Months 2, 6 and 12 will also be presented with the estimate, standard error and 95% CI. If the treatment effect is significant at the 10% level then the treatment means will be compared using the least significant difference (LSD) method and the p-value presented.

The change from baseline in foveal encroachment will be summarized by treatment group and visit for the MITT population using the observe data. Summaries will present the descriptive statistics

for baseline, absolute values and change from baseline data.

The observed mean change from baseline in distance of GA lesion from fovea with ± SE of mean change, will be plotted over time by treatment group.

8.2.6. Drusen Size

Study eye drusen size (none, small, intermediate or large) and number of intermediate/large drusen collected at baseline and end of study will be summarized by treatment group for the MITT population with a shift table relative to baseline. Marginal totals will be included and missing data will also be summarized. The end of study visit will be summarized including and excluding subjects who discontinued treatment early.

8.2.7. GA Lesion Size Measured by SD-OCT

The change from baseline in square root area for GA lesion over time to Month 12 as measured by SD-OCT will be analysed for the subset of subjects who have data, in the same way as the primary endpoint for the MITT population.

The analysis model table will be presented. The treatment comparisons (AM vs Sham, AEOM vs Sham and AM vs AEOM) at Months 2, 6 and 12 will also be presented with the estimate, standard error and 95% CI. If the treatment effect is significant at the 10% level then the treatment means will be compared using the least significant difference (LSD) method and the p-value presented.

The change from baseline in square root area for GA lesion will be summarized by treatment group and visit for the MITT population using the observe data Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data.

8.2.8. Genetic Polymorphisms

Genetic marker analysis will be performed by The Institute of Human Genetics at the University of Regensburg. The relationship of the primary endpoint and each gene will be investigated. The analysis will be documented in a separate report and included in the CSR as an appendix.

8.2.9. Other Ophthalmology Data

All other ophthalmology data collected but not discussed in other sections of the SAP will be listed by treatment group. The ophthalmology assessments performed in this study include the following:

- Fundus Autofluorescence Photographs (FAF)
- SD-OCT
- Digital Color Fundus Photographs (DCFP)
- Fundus Fluorescein Angiograms (FFA)

- Infrared Reflectance (IR)
- BCVA and LL-BCVA

9. ANALYSIS OF PHARMACOKINETICS

9.1. CONCENTRATION DATA

The APL-2 trough concentrations will be evaluated using the PK population. APL-2 trough concentrations will be summarized by treatment group at each protocol specified time point using descriptive statistics including the interquartile range. The number of subjects with a BLQ value will also be tabulated.

Linear and log-linear individual trough concentration profile plots against time will be produced for each APL-2 treatment group. The actual sampling time will be used on the x-axis.

Linear and log-linear median trough concentration profile plots against time will be produced by treatment group. The nominal sampling time will be used on the x-axis.

A listing of all trough concentration data will be presented by treatment group.

9.2. PHARAMCOKINETIC DATA

C_{max} should occur at Day 7 ($C_{Day\ 7}$), which will be listed and summarized as part of the concentration data. No additional presentations are required.

10. ANALYSIS OF PHARMACODYNAMICS

The PD parameters (CH50 and C3) will be evaluated using the PD population. Absolute values, changes from baseline and percentage changes from baseline for the PD parameters will be summarised by treatment group at each protocol specified time point using descriptive statistics.

For each PD parameter, the individual absolute values and individual changes from baseline will be presented graphically for each treatment group. Actual sampling times will be used for the graphical presentation of individual data.

The mean absolute values, mean changes from baseline and mean percentage changes from baseline will also be presented graphically by treatment group. Nominal sampling times will be used for the mean plots.

Individual PD parameters will be listed together with changes from baseline and percentage changes from baseline by treatment group.

11. SAFETY

All safety evaluation will be performed on the safety population.

11.1. ADVERSE EVENTS

AEs will be summarized separately for those occurred in the study eye, those in the fellow eye, and the non-ocular events.

AEs will be coded using the latest MedDRA version available.

According to the completion guidelines for this study any AE recorded prior to first dose of study drug should be recorded on the medical or ocular history page instead. So, all AEs recorded should be treatment emergent AEs (TEAE). However, a check will be made and AEs will be considered treatment-emergent unless there is clear indication that the event occurred prior to the first dose of study drug. AEs present prior to study drug administration that increased in severity or relationship to study drug after the first dose of study drug and up to 60 days beyond the last dose of study drug will be classed as TEAE. Events with missing or partial dates will be handled such that in the absence of contradictory information an AE is treatment emergent. So, for a missing start date (where stop date is after first dosing date or missing) the date will be imputed as the first dose date; for a missing stop date the date will be imputed as the last study date. If a partial date is recorded, the following convention will be used to assign the AE:

- If a start date is missing the day information and month/year is the same as first dose date then use first dose date, else '01' will be used for the day; if a start date is missing the month and the year is the same as first dose date then use first dose date, else January will be used for the start month.
- If a stop date is missing the day information and month/year is same as last study date then use last study date, else last day of the given month will be used for the stop day; if a stop date is missing the month and year is the same as last study date then use last study date, else December will be used for the stop month.

Only TEAEs will be included in the summary tables. An overall summary will present the number of subjects by treatment group and overall with:

- any TEAE
- any TEAE considered as related to study drug (evaluated by the investigator as Possibly Related or Probably Related or not reported)
- any serious TEAE
- any treatment emergent AESI (TEAESI) in either eye
- any TEAESI in study eye
- Maximum severity TEAE of none, mild, moderate, severe, life-threatening, death ; i.e. a subject with TEAEs at different intensities will be summarized at the most severe intensity

- any TEAE leading to study drug discontinuation
- any TEAE leading to death

The table will also include the total number of TEAEs reported and total number of TEAESI reported. The total number of unique terms within subjects will also be presented, counting each TEAE only once within each subject.

The number and percentage of subjects with TEAEs will be presented by SOC, PT and by treatment group and overall. Subjects with multiple TEAEs within a SOC or SOC/PT combination will be counted only once for that SOC or SOC/PT combination. Similar summaries will be presented for related TEAEs, TEAEs leading to discontinuation, serious TEAEs and TEAESI in study eye.

Summaries of TEAEs by maximum severity (mild, moderate, severe, Life-threatening or death) will be presented. This will be repeated for TEAESI in study eye.

All summaries will be ordered by descending order of total events in the APL-2 pooled group.

All TEAEs will be listed by treatment group, subject and AE onset date. Separate listings of serious AEs, AESI and AEs leading to discontinuation of study drug will also be generated. For the listing of AESI the effected eye (study or fellow) will also be listed.

11.2. INTRA OCULAR PRESSURE (IOP)

The observed and change from baseline values in IOP over time will be summarized by treatment group and protocol specified time points for the safety population. Summaries will present the descriptive statistics for baseline and change from baseline data. The acute change in IOP after each injection (i.e., change from pre-injection to post-injection value) will also be summarized at each protocol specified time point.

The number of subjects with IOP ≥30 mmHg post injection will be summarized by treatment group, visit and over the whole study.

11.3. ANTERIOR SEGMENT EXAMINATION

Anterior segment examination endpoints (abnormal reaction to light, active inflammation present in cornea, abnormal anterior chamber, any opacity in lens, aqueous reaction flare and aqueous reaction cells) will be summarized separately for the study eye and the fellow eye by treatment group and protocol specified time points for the MITT population, using summary statistics for categorical variables.

11.4. POSTERIOR SEGMENT EXAMINATION

Posterior segment examination endpoints (posterior segment abnormalities, presence of posterior vitreous detachment, presence of retinal hemorrhage/detachment, vitreal hemorrhage density and vitreous cells evaluation) will be summarized separately for the study eye and the fellow eye by

treatment group and protocol specified time points for the MITT population, using summary statistics for categorical variables.

All other ophthalmology data collected based on Slit Lamp and Dilated Binocular Indirect Ophthalmoscopy examinations but not discussed in other sections of the SAP will be listed by treatment group.

11.5. LOCS III LENS

The observed and change from baseline values for each of the 4 endpoints (nuclear opalescence, nuclear color, cortical cataract and posterior subscapular cataract) will be summarized by treatment group and protocol specified time points, for those subjects with LOCS III performed during the study. The denominator for this summary will be the subset of phakic subjects who have a LOCS III assessment performed at any time during the study. The number of pseudophakic and aphakic subjects will also be presented.

All individual LOCS III data will be listed by treatment group. The listing will include change from baseline values. If no baseline value is collected and the baseline anterior segment assessment confirms no opacity in the lens then a value of 0.1 will be used for baseline and the change from baseline value will be flagged to identify the imputation.

11.6. LABORATORY EVALUATIONS

Observed and change from baseline clinical laboratory data (hematology, chemistry and urinalysis) will be summarized by treatment group and protocol specified time points. Urinalysis categorical data will also be summarized by treatment group and protocol specified time points. Descriptive statistics will be used for continuous data and frequency counts and percentages for categorical data. A shift table from baseline, by treatment group and protocol specified time points, of normal, abnormal low, abnormal high and missing records will also be summarised for hematology and chemistry data with marginal totals using frequency counts and percentages.

All individual laboratory results will be listed by treatment group. The listing will include change from baseline values and values outside the laboratory reference range will be flagged.

11.7. ANTIGENICITY DATA

Summaries of antigenicity data (titre, specificity and immuno-reactivity) by treatment group and protocol specified time point will be presented. Descriptive statistics will be used for specificity data and frequency counts and percentages for titre (< 5 or 5) and immuno-reactivity (non-reactive or reactive) data.

Antigenicity data will be listed by treatment group.

11.8. VITAL SIGNS

Observed and change from baseline values will be summarized for all vital signs data (blood pressure, heart rate, respiratory rate and temperature) by treatment group and protocol specified time points using descriptive statistics.

Vital signs data will be listed by treatment group.

12. INTERIM ANALYSES

A Month 12 cut of the data will be analysed and reported in the CSR. When all subjects have completed (or discontinued) the 12 Month assessment visit the data collected up to and including these study visits will be cleaned and reported. The exception to this will be SAEs and AESI where all available events up to the last subjects Month 12 visit date will be included in the report. Any changes to the data reported in this Month 12 cut will be fully auditable and discussed in the addendum to CSR that will be generated on the final 18-month study data.

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 AESI. Additional regular or ad-hoc safety reviews will be scheduled as recommended by the SMC.

13. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

The changes from the analyses specified in the protocol are:

1. The definition of the PP population has been updated to exclude any subject who has violated any inclusion or exclusion criteria and/or deviated from the protocol, in a way that could influence their efficacy assessment. The protocol refers to the PP as all randomized subjects who return for 12 month visit which is simply a completer's analysis which is covered in the sensitivity analyses of the primary endpoint.

2. The primary analysis specified in the protocol does not take account of baseline in the model, however as a precaution baseline has been included in the model. If there is no relationship with baseline then only one degree of freedom is lost by including this term in the model.

3. The protocol specified the use of ANOVA on the data at Month 12 with missing data handled by the LOCF or by a non-precise regression method of imputation when imbalance drop-out rates occur across treatment groups. An MMRM approach, which directly utilizes

all available data in the model, has been specified in the SAP to account for missing data and this will be regarded as the primary analysis.

4. The pharmacokinetic endpoints of AUC, C_{max}, T_{max} and $t_{1/2}$ were specified in the protocol; however since only trough concentrations were collected throughout the study it is only possible to assess C_{max}. C_{max} should occur at Day 7 so the concentration on Day 7 will be used ($C_{Day\ 7}$).

5. The protocol specified a standard deviation of annual square root area growth of 0.21mm/year for the sample size calculations. However in the power analysis (protocol Section 11.3.3) a value of 0.2 was used for the standard deviation.

6. The protocol refers to the first day of dosing as Day 0 (Visit 2). For reporting purposes CDISC standards will be used and therefore it is necessary to refer to the first day of dosing as Day 1. Consequently throughout the SAP Day 1 is referred to as the first day of dosing.

14. REFERENCES

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