Statistical Analysis Plan

Study Title:	An 18-Month Phase Ib/II Multi-Center, Open Label Study to Evaluate the Safety of Intravitreal APL-2 Therapy in Patients with Neovascular Age-Related Macular Degeneration (AMD)
Protocol Number:	APL2-203
Amendment	Version 3.0 / 03 Aug 2018
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1.0	03 Jul 2019	Original Document

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1. LIST OF ABBREVIATIONS AND ACRONYMS

Abbreviations and Acronyms	Description
ADaM	Analysis Data Model
ADDV	ADaM Data Structure for Protocol Deviation Analysis
AE	Adverse Event
AESI	Adverse Event of Special Interest
AMD	Age-related Macular Degeneration
Anti-VEGF	Anti-Vascular Endothelial Growth Factor
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
bpm	beats per minute
BQL	Below-Quantification-Level
°C	Degrees Celsius
CFB	Change From Baseline
CNV	Choroidal Neovascularization
DCFP	Digital Color Fundus Photographs
DPC	DP Clinical Inc.
eCRF	Electronic Case Report Form
FFA/FA	Fundus Fluorescein Angiograms or Fluorescein Angiography
ICH	International Council for Harmonisation
IOP	Intra Ocular Pressure
ITT	Intent-to-Treat
IVT	Intravitreal
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeter of Mercury
OCT	Optical Coherence Tomography
ODS	Output Delivery System
QC	Quality Control
PCFB	Percent Change From Baseline

Abbreviations and Acronyms	Description
PRN	Pro re nata (As Needed)
PT	Preferred Term
RPE	Retinal Pigment Epithelium
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SDTM	Study Data Tabulation Model
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedure
Sub-RPE	sub-Retinal Pigment Epithelium
TEAE	Treatment-Emergent Adverse Event
TLFs	Tables, Listings and Figures
VAS	Visual Acuity Score
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization
WHODrug	World Health Organization Drug Dictionary
WOCBP	Woman of Child Bearing Potential

2. INTRODUCTION

This Statistical Analysis Plan (SAP) is prepared to provide a more technical and detailed elaboration of the principal statistical features stated in the protocol. The SAP will ensure that the tables, listings, and figures that will be produced and statistical methods that will be used are complete and accurate and will allow valid conclusions to be drawn. In the development of this SAP, the following study documents were used:

1. Protocol APL2-203 Version 1.0, 20 December 2017
2. Protocol APL2-203 Version 1.1, 03 January 2018
3. Protocol APL2-203 Version 2.0, 14 March 2018
4. Protocol APL2-203 Version 3.0, 03 August 2018
5. Electronic Case Report Form (eCRF), 18 March 2019
6. Medical Coding Guidelines Version 1.0, 19 March 2018

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

- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E3 (ICH 1995): Structure and Content of Clinical Study Reports
- ICH E6 R2 (ICH 2016): Guideline for Good Clinical Practice - Integrated Addendum to ICH E6 (R1).
- ICH E9 (ICH 1998): Statistical Principles for Clinical Trials

In the event that a discrepancy is found between the descriptions in the statistical section of the protocol and this document, the description in this document supersedes the descriptions in the statistical section of the protocol. Any deviations from the final analysis plan or from what is outlined in the protocol will be discussed in the final study report.

3. STUDY OVERVIEW

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

3.1 Objective

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

3.2 Endpoints

3.2.1 Primary Endpoint

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

3.2.2 Secondary Endpoints

- Changes from baseline in laboratory parameters
- Changes from baseline in central macular thickness on Optical Coherence Tomography (OCT) over 12 months

3.2.3 Exploratory Endpoint

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

3.3 Study Design

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

Patients will initially be screened between Day -28 and prior to treatment on Day 1. Screening procedures will include laboratory tests, Best Corrected Visual Acuity (BCVA), ophthalmological exam, Intraocular Pressure (IOP), and Spectral Domain Optical Coherence Tomography (SD-OCT). Upon entry into

the study (after signing the informed consent), subjects will be assigned a screening number. At screening visit 1 (Day -28) subjects will have an SD-OCT taken to assess for the presence of any subretinal, intraretinal, or sub-Retinal Pigment Epithelium (sub-RPE) fluid, followed by an IVT dose of an anti-VEGF drug. Subjects will return two weeks later for screening visit 2 (Day -14) and will have another OCT performed to confirm a decrease in excess fluid in the macula. Upon confirmation by the Investigator of fluid reduction, subjects who meet all inclusion and exclusion criteria will be enrolled in the study and will return at Day 1 for treatment (Visit 3; Day 1). Treatment on Day 1 will entail a mandatory IVT dose of an anti-VEGF drug followed by an IVT injection of APL-2.

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

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

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

Study Assessments align with those described in Section 12 of the Clinical Study Protocol (Version 3.0), 03 Aug 2018.

3.3.1 Sample Size Considerations

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

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

3.3.2 Study Assessments Schedules

The study assessment schedule is described in detail in Section 11 of the protocol (Version 3.0), and summarized in Study Flow Charts in Appendix Section 8.1.

4. GENERAL CONSIDERATIONS

4.1 Definitions

4.1.1 Study Day

Study Day 1 will be the day a subject takes the first dose of APL-2. Study days will be calculated as:

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

Study Day = visit date – date of administration of first APL-2 dose + 1

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

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

4.1.2 Baseline and Change from Baseline

In general, the baseline for this study will be taken as the pre-dose measure on Study Day 1. If this is missing then the closest assessment prior to the baseline will be used, if available.

Unless indicated otherwise change from baseline (CFB) will be calculated as follows:

CFB = Visit Result – Baseline Result

Percent change from baseline (PCFB) will be calculated as follow:

PCFB (%) = 100(Visit Result – Baseline Result)/Baseline Results*

4.2 Analysis Data Sets

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

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

Screened Set:

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

Safety / Intent-to-Treat (ITT) Set:

The safety analysis set will include all patients who receive a dose of APL-2. The ITT set will be identical to the safety analysis set for this study.

4.3 Test Hypothesis and *P*-Value Justification

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

4.4 Procedures for Handling Missing Data and Dropouts

4.4.1 Safety Data

Where appropriate, screening values may be used as baseline in the event of missing or unusable Day 1 measurements. No imputation of missing data for early terminations will be performed.

However, both partial and completely missing dates/times that are not related to early terminations, in addition to missing safety data (e.g., missing severities) will be reviewed on a case by case basis for potential imputations. As a general rule, a conservative approach will be adopted as outlined in Section 5.2.1 (e.g. partial Adverse Event (AE) onset dates and missing severities will be taken as the earliest 'on treatment' start date and highest severity, respectively, consistent with the partial information available). Moreover, the original data, without imputations, will be presented separately in data listings.

For safety lab parameters that are below or above the limit of quantification, the data will be presented as-is in the listings, but the limit of quantification will be used for the purposes of calculating changes from baseline.

4.4.2 Visit Windowing Based on Study Day

Unless otherwise noted (See Section 5.2.9: Fundus Fluorescein Angiogram, Section 5.2.10: Digital Fundus Photography), unscheduled assessments that occur during on-study days that are within a scheduled visit window per the "Window (+ or - Days)" specifications in the schedule of assessments in Appendix 8.1 will be mapped to the scheduled visit name for summary tables. Subjects who complete the Early Termination visit within a scheduled visit window will be mapped to the scheduled visit for summary tables. Early Termination assessments that do not fall within a scheduled visit window will not be windowed.

Original non-windowed visit information as-collected will be presented in the listings. The windowed visits, where applicable, will be displayed alongside the visit information as-collected in the listings.

4.5 Interim Analysis

No interim analysis will be performed in this study.

4.6 Subgroup Analysis

Due to the small sample size of the study, no subgroup analyses will occur.

4.7 Multi-Center Studies and Pooling of Centers

This is a multi-center study. Due to the small number of subjects at each site, no adjustments will be made for study site.

5. STATISTICAL ANALYSIS METHODOLOGY

In general, since there is one cohort in the study, tables will be presented for the overall population.

Tabulations for continuous data will use a standard set of descriptive statistics: number of observations available (n), mean, standard deviation (SD), median, and range (minimum, maximum).

Categorical or dichotomous data will be tabulated using frequencies (counts and percentages). The numerator and denominator for each percentage calculation will be specified in the footnotes of table shells.

Data listings will present all information recorded in eCRFs for all subjects and visits. All listings will be sorted by subject number.

5.1 Study Subjects

5.1.1 Subject Disposition

The following disposition categories will be tabulated:

- Number of subjects screened
- Number of screen failures with reason for screen failure
- Number of subjects that terminated the study prior to study drug
- Number of subjects who receive at least at least one dose of APL-2 (Safety Population/ITT Population)
- Number of subjects who complete Treatment Phase – subjects who complete through Visit 15
- Number of early termination subjects during Treatment Phase (subjects who do not complete Visit 15) with reason for early termination
- Number of subjects who complete Follow-Up through Visit 17

5.1.2 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedure defined in the protocol.

The following categories will be used to group protocol deviations:

1. Eligibility Not Met
2. Study Assessment Noncompliance
3. Study Drug Noncompliance
4. Study Schedule Noncompliance
5. Other

The following are categorical reasons used to document why a protocol deviation occurred:

1. Subject Illness
2. Subject Unable to Comply
3. Subject Refusal
4. Clinical/Site Error
5. Laboratory Error
6. Investigator/Staff decision
7. Other

Subsets of the protocol deviations can be identified as major and minor protocol deviation as described below:

Major Protocol Deviation: A protocol deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

Minor Protocol Deviation: A protocol deviation that will not significantly affect the completeness, accuracy, and/or reliability of the study data and that will not significantly affect a subject's rights, safety, or well-being.

Upon soft lock of database, all documented protocol deviations in the study will be reviewed to identify all major and minor protocol

deviations by a data review team including representatives from DPC clinical operations, medical, data management, and statistics, and sent to the sponsor for approval. Final decisions will be documented and incorporated into the ADaM Data Structure for Protocol Deviation Analysis (ADDV) dataset.

Protocol deviation data will be presented for the safety population. Protocol deviations and major protocol deviations will be summarized in listings. Additionally, the number of deviations and frequency of subjects with protocol deviations and with major protocol deviations will be tabulated. The number of deviations and frequency of subjects with each protocol deviation category will also be tabulated.

5.1.3 Medical and Surgical History

At Screening Visit 1, the general medical and surgical procedures history will be recorded on the eCRF, all medical/surgical history data and ongoing medical history will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 System Organ Class (SOC) and Preferred Term (PT).

5.1.4 Prior and Concomitant Medications

Prior and concomitant medications will be coded to the therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug Dictionary (WHODrug) classifications version March 2017.

Prior medications will include any medications reported with a start date prior to the subject taking their first study dose and will be summarized by WHODrug Anatomical Therapeutic Chemical (ATC) Class 1 Term and WHODrug Preferred Name. Concomitant medications will include any medications being taken after the subject starts their study medication and will also be summarized by WHODrug ATC Class 1 Term and WHODrug Preferred Name.

Hence, medications ongoing at the start of dosing will be counted in both the prior and concomitant medication summaries.

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

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

All prior medications and concomitant medications, interventions and procedures will be summarized in listings. The frequency of subjects taking prior medications and concomitant medications will be tabulated by WHODrug ATC Class 1 and Preferred Name.

Concomitant procedures will be summarized in a listing.

5.1.5 Exposure

All study drug exposure data will be listed based on the Study Drug Administration eCRF.

The frequency of subjects who receive a study drug injection will be summarized by visit for Visits 3 through 15.

5.2 Safety Analysis

The objective of the study is to establish the safety and tolerability of intravitreally injected APL-2 in patients with neovascular AMD. The safety analyses will be performed on the safety analysis set.

5.2.1 Adverse Events

Treatment emergent adverse events (TEAE) are defined as those AEs that develop or worsen after the first dose of study medication, up to 30 days beyond the last dose of study medication. Version 20.0 of MedDRA will be used to classify all AEs.

AEs will be considered treatment-emergent (TEAE) unless there is clear indication that the event occurred prior to first dose of study drug. AEs present prior to the first dose of study drug administration that increased in severity or relationship to study drug after the first dose of study drug and up to 30 days beyond the last dose of study drug will be classed as a TEAE. Events with missing or partial dates will be handled such that in the absence of contradictory information an AE is treatment emergent. So for a missing start date (where stop date is after date of first dose) the date will be imputed as the date of first dose; for a missing stop date the date will be imputed as the last study date. If a partial date is recorded, the following convention will be used to assign the AE:

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

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

Adverse Events Summary

A TEAE data listing, including verbatim term, preferred term, treatment, severity, and relationship to treatment will be provided. Serious Adverse Events (SAEs), adverse events of special interest, and details of subjects withdrawing due to adverse events will also be listed. The start and stop days (relative to the first dosing day), onset time since last dose, and the duration of AEs will be included in listings.

A topline summary for the overall time on study will present the number of events and the frequency of subjects with:

- any TEAE
- any TEAE considered as related to study drug (evaluated by the investigator as Possibly Related, Probably Related, Definitely Related, or not reported)
- any TEAE considered as related to injection procedure (evaluated by the investigator as Possibly Related, Probably Related, Definitely Related, or not reported)
- any serious TEAE
- Maximum intensity TEAE of none, mild, moderate, severe, life threatening, and 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 overall, total number of reported TEAEs. The total number of unique terms within subjects will also be presented, counting each TEAE only once within each subject.

Additionally, the following will be tabulated with the number of events and the frequency of subjects. Summaries will be ordered by descending order of event count in the overall column.

- Non-ocular TEAEs by SOC and preferred term
- Ocular TEAEs by SOC and preferred term by Study Eye and Fellow Eye
- TEAEs regarded as at least possibly related to study drug by SOC and preferred term
- TEAEs regarded as at least possibly related to injection procedure by SOC and preferred term
- Non-ocular TEAE related to study drug or injection procedure by SOC and preferred term

The following will also be tabulated with only the frequency of subjects:

- Non-ocular TEAEs and Serious AEs by SOC, preferred term, and maximum severity
- Ocular TEAEs and Serious AEs by SOC, preferred term, and maximum severity by Study Eye and Fellow Eye

5.2.2 Clinical Laboratory Tests

Laboratory values outside the reference range will be identified in listings, using flags to identify whether above or below the range limits. Hematology, Serum Chemistry, and Urinalysis results will be presented separately.

Listings of all lab results and out of range lab results with their corresponding changes from baseline will be presented. Baseline will be considered as the collection on Screening Visit 2..

A table of descriptive statistics will be presented for continuous chemistry, hematology, and urinalysis laboratory results. The number

and percent of subjects with low, normal, and high assessments at each scheduled visit will be tabulated by lab parameter.

5.2.3 Vital Signs

The listing of vital sign data will include change from baselines. Baseline will be considered the Study Day 1 pre-dose assessment or the last dose prior to Study Day 1 if missing the Study Day 1 assessment. In the listing, data fulfilling the following criteria will be flagged:

Value	Parameter	Low	High
Observed	Systolic Blood Pressure (mmHg)	≤ 80	≥165
	Diastolic Blood Pressure (mmHg)	≤ 40	≥ 95
	Pulse (bpm)	≤ 40	≥120
	Temperature (^{o}C)		≥ 38

*mmHg=millimeters of mercury, bpm=beats per minute, ^{o}C=degrees Celsius

A table of descriptive statistics will be presented for each vital sign parameter. The number and percent of subjects with low, normal, and high assessments at each scheduled visit will be tabulated.

5.2.4 Physical Examination

Physical examination data will be listed.

5.2.5 Complete Ophthalmic Examination

Complete ophthalmic exams will be performed at pre-dose visits during the treatment period, including an examination of the eyelids and pupils, iris evaluation, cornea evaluation, anterior chamber evaluation, and lens evaluation. Results will be listed.

The following shift tables will be produced at each visit for the study eye, with the Study Day 1 pre-dose assessment as baseline, or the last assessment before Study Day 1 if not available:

- External Examination of Eye (Normal / Abnormal)
- Exam of Eyelids and Pupils
  - Ptosis Present (Yes / No)
  - Abnormal Pupil Shape (Yes / No)
  - Unequal Pupils (Yes / No)
  - Abnormal Reaction to Light (Yes / No)
  - Afferent Pupillary Defect (Yes / No)
- Iris Evaluation (Normal / Abnormal)
- Cornea Evaluation (Normal / Abnormal)
- Anterior Chamber Evaluation
  - Anterior Chamber (Normal / Abnormal)
  - Cells (0 / Trace / 1+ / 2-3+ / 4+)
  - Flare (0 / Trace / 1+ / 2+ / 3+ / 4+)
- Lens Evaluation (No Opacity / Nuclear Sclerotic Cataract / Posterior Subcapsular Cataract / Cortical Cataract / Pseudophakia / Aphakia)

5.2.6 Intraocular Pressure

Intraocular pressure (IOP) with change from baseline will be listed across Study Day 1 through Study Day 540, where baseline will be the Study Day 1 pre-dose assessment, or the Screening Study Day -14 assessment if not available.

Additionally IOP will be summarized at each scheduled visit using descriptive statistics for pre-injection IOP and change from baseline. Additionally, the frequency of the following will be tabulated:

- Subjects with pre-first-injection IOP > 21 mmHg
- Subjects with post-injection IOP > 30 mmHg at any post-baseline visit where an injection was received

- Subjects that underwent anterior chamber paracentesis procedure, as determined by a Concomitant Procedure term = "Anterior chamber paracentesis"
- Subjects that developed AE of ocular hypertension and/or glaucoma, as determined by an AE with MedDRA SOC "Eye disorder" and one of the following preferred terms: "borderline glaucoma," "glaucoma," "normal tension glaucoma," "ocular hypertension."

5.2.7 Best Corrected Visual Acuity

The BCVA assessments will be listed for each eye, including sphere sign for values not equal to 0, sphere value, cylinder sign for values not equal to 0, cylinder value, axis, BCVA at 1 meter (BCVA1), BCVA at 4 meters, Total Visual Acuity Score (VAS), and Snellen equivalent. The Total VAS will be listed with change from baseline, where the Study Day 1 pre-dose assessment will be considered baseline, or the last assessment prior to Study Day 1 if not available.

The Total VAS will be summarized in a table using descriptive statistics by scheduled visit. The mean VAS score (± 2 x SD) will be plotted by scheduled visit. The number of subjects evaluable at each visit will be visible on the plot. Additionally, the frequency of the following will be tabulated:

- Subjects that lost ≥15 letters compared to baseline (CFB ≤ -15) at any visit
- Subjects that lost ≥35 letters compared to baseline (CFB ≤ -30) at any visit

5.2.8 Dilated Indirect Ophthalmoscopy

Dilated indirect ophthalmoscopy will be performed from Study Day 1 (Visit 2) though the end of study (Visit 17). All results will be listed.

The following shift tables will be produced at each visit for the study eye, with the Study Day 1 pre-dose assessment as baseline, or last assessment prior to Study Day 1 if not available.:

- Posterior Segment Abnormalities (None / Mild / Moderate / Severe)
- Posterior Vitreous Detachment (Absent / Present)
- Retinal Hemorrhage/Detachment (Absent / Present)
- Vitreal Hemorrhage Density (None / 1+ / 2+ / 3+ / 4+)
- Vitreous Cells (0 / Trace / 1 / 2 / 3 / 4)

5.2.9 Fundus Fluorescein Angiograms

Fundus Fluorescein Angiograms (FFA) results will be listed. If the parameter is reported as a numeric value, the change from baseline and percent change from baseline will be reported in the listing.

Frequency of the following parameters in the study eye will be tabulated by for the pre-dose Study Day 1 assessment (Baseline) and for the Visit 15 or Early Termination assessment:

- Choroidal Neovascularization (CNV) (Yes / No / Cannot Grade)
- CNV Classification (Occult / Disciform Scar / Cannot Grade) – this will be tabulated only for subjects with CNV
- CNV Classification Detail (CNV Within Image Frame) – this will only be tabulated for subjects with CNV and with a gradable classification

Descriptive statistics will be tabulated for the following parameters in the study eye for the pre-dose Study Day 1 assessment (baseline) and for the Visit 15 or Early Termination assessment:

- Total CNV Area
- Total Lesion Area
- Disciform Scar Area

For the purposes of the summary tables above, all ET visits will be summarized together.

5.2.10 Digital Color Fundus Photographs

Digital Color Fundus Photographs (DCFP) data will be listed. The frequency of responses will be tabulated for the following DCFP parameters in the study eye for the pre-dose Study Day 1 assessment (Baseline) and for the Visit 15 or Early Termination assessment:

- Atrophy (Yes / No / Cannot Grade)
- Atrophy Areas (Single / Multiple / Cannot Grade)
- Intraretinal Hemorrhage (Yes / No / Cannot Grade)
- Intraretinal Hemorrhage Location (Foveal / Macular)
- Subretinal Fluid (Yes / No / Cannot Grade)
- Subretinal Fluid Location (Foveal / Macular)
- Subretinal Sub-Retinal Pigment Epithelium (RPE) Hemorrhage (Yes / No / Cannot Grade)
- Subretinal Sub-RPE Hemorrhage Location (Foveal / Macular)

For the purposes of the summary table above, all ET visits will be summarized together.

5.3 Other Analyses

The following analyses will be performed on the ITT population.

5.3.1 Spectral Domain Optical Coherence Tomography (SD-OCT)

All Spectral Domain Optical Coherence Tomography (SD-OCT) parameters will be summarized. If the parameter is reported as a numeric value, the change from baseline and percent change from baseline will be reported in the listing.

The Study Day 1 pre-dose assessment will be considered as baseline, or the last assessment before the first dose of APL-2 will be used if it is not available.

Central subfield thickness, cube volume, pigment epithelial detachment thickness, and subretinal fluid thickness will be summarized for the study eye in tables with descriptive statistics for the overall intent-to-treat population at each visit. For each visit, change from baseline and percent change from baseline (when the baseline is not equal to zero) will be calculated.

5.3.2 Anti-Vascular Endothelial Growth Factor (anti-VEGF) As-Needed Injections

The frequency of subjects who receive an anti-VEGF injection will be summarized by visit for Visits 4 through 17.

5.4 Immunogenicity

Immunogenicity data will be presented in a listing.

6. TESTING/QUALITY CONTROL PLAN AND SOFTWARE/SYSTEM

All statistical programs, will be written in SAS® version 9.3 or higher. Statistical programs will be tested and reviewed for Quality Control (QC) by a second programmer/biostatistician not involved in the programming as per DPC's standard operating procedure (SOP). In addition, DPC's SOP will be followed to ensure that the information is complete, consistent, and accurately reflects the data stored in the database. Further all TLFs will undergo a QC process by an independent biostatistician/programmer to ensure that the information is complete, consistent, and accurately reflects the data.

6.1 Programming Specifications for TLFs

Appendix 8.1 provides a list of all the TLFs that are planned to be produced.

6.2 Formatting Conventions

The following formatting conventions will be used to output TLFs:

- TLFs are outputted by SAS Output Delivery System (ODS) into Rich Text Files (RTF) format.
- Tables and Listings will include borders around all headings and data cells.
- Output will be in landscape orientation with margins of 0.5 inches on top, right, and left, and 1 inch for bottom.
- The default font to be in tables/listings/figures will be Courier New.
- Preferred and minimum font size:

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

- Data will be centered within columns when the maximum length of the data being displayed is less than or equal to the maximum width of the column heading. When the maximum length of the data being displayed exceeds the maximum width of the column heading, the data will be left-justified.
- Column headings should be in initial capital characters. For numeric variables, include "unit" in the column heading when appropriate.
- In figures, axes will be labeled appropriately.

6.3 Standard Text Conventions

6.3.1 Header

All output (table, listing, or figure) will have the following header, as applicable:

```
Apellis Pharmaceuticals, Inc.
Protocol: APL2-203                                          Page xx of XX
Clinical Study Report
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All output will have the date and time (date and time output was generated) and internal page number in the header. Tables/Listings/Figures should be internally paginated (i.e., page numbers should appear sequentially within each output).

6.3.2 Title

At least three (3) lines, in general, will be reserved for the entire title.

- The first line is for the table/listing/figure number;
- The second line is for the actual title; and
- The third line is reserved for the analysis population descriptor.

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

```
                    Table 14.3.1.1
          Topline Summary of Adverse Events
                  Safety Population
```

6.3.3 Footnotes

Unless otherwise specified, footnotes will appear on all pages within the tables and listings as follows:

- Footnotes will be in the format of "NOTE: followed by 2 spaces, then the footnotes", as shown in the following example:

```
NOTE:  SD = Standard Deviation.
```

- Each line of a complete footnote should end with a period.
- When an abbreviation (e.g. AE, SAE, etc.) appears first time in the whole set of TLFs for a study, a footnote should be provided at least once; and it is up to the study statistician, to decide whether there is a need to repeat the same footnote for the rest of TLFs.
- A footnote serves as a brief explanation/clarification /definition /concept of a flag symbol or a character, an abbreviation, a terminology, etc., that appears in or relates directly to the displayed content of a table/listing/figure.
- All footnotes will be at the lowest line of the page immediately above the footer. The footer will be directly on the line below the last footnote.
- For Tables, first footnote will provide source listings and/or analysis datasets names for cross-referencing.

6.3.4 Footer

The following footer should appear at the very bottom of each page of a table, a listing, or a figure generated in SAS in the lower left corner:

```
Program Name: PGNAME.sas; Creation Date and Time: DDMMMYYYY HH:MM
Data Cutoff DDMMMYYYY HH:MM - ADaM Generated DDMMMYYYY          Proprietary and Confidential
```

where PGNAME = SAS program name.

6.4 Statistical Conventions

6.4.1 Statistics Reported

- Unless otherwise specified, the mean and SD will be displayed to one more decimal place than the original value, while minimum and maximum will be reported in the format of the original data, e.g.:

  Original: xx

  Mean and SD: xx.x

  Minimum and maximum: xx

- Use of N versus n:

  N = total number of subjects or subjects in the population.

  n = total number of subjects or subjects in the specific category.

- Descriptive statistics in this template include: N. Mean, Median, SD, Minimum, and Maximum.
- Unless specified in the actual TLF shells for a study, all percentages will be rounded to 1 decimal place in all tables/listings/figures. Rounding will take place after all calculations have been performed.

6.4.2 Tables Summarizing Categorical Data

The following specifications apply to tables that summarize categorical data:

- If the categories of a parameter are ordered, then all categories between the maximum possible category and the minimum category will be included, even if n=0 for a given category between the minimum and maximum level for that parameter.
- If the categories are not ordered, then only those categories for which there is at least one subject represented will be included.
- A missing category will be added to any parameter for which information is not available for any subjects.

6.4.3 Subject Data Listings

In general, individual subject data listings will include the data of all non-screen failure subjects. However, if a subject data listing includes only subjects who met a certain condition, and there were no subjects who met that condition, then a "message" will appear indicating that no subjects met the condition for inclusion in that listing. Data listings will provide the derived study day of an assessment or event, where appropriate.

7. REFERENCES

ICH E3 (1995): Structure and Content of Clinical Study Reports. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

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MedDRA Version 20.0 (March 2017). International Federation of Pharmaceutical Manufacturers and Associations (IFPMA).

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

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The WHO Drug Dictionary (WHO-DD) (March 2017). World Health Organization (WHO) Uppsala Monitoring Center (UMC).

8. APPENDICES

8.1 Schedule of Events

	Screening		Treatment													Follow-Up		Early Term. [A]
Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
Day	-28	-14	1	30	60	90	120	150	180	210	240	270	300	330	360	450	540	
Week	0	0	0	4	8	12	16	20	24	28	32	36	40	44	48	60	72	
Month	0	0	0	1	2	3	4	5	6	7	8	9	10	11	12	15	18	
Window (+ or - days)	2	3	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	
Informed Consent / Assign Screening Number	x																	
Demographic Data	x																	
Inclusion/Exclusion Criteria [B]	x	x	x															
Medical/Surgical/Ophthalmic History [C]	x																	
Blood Draw – Safety Labs [D,E]		x		x					x						x			x
Urine Sample Collection [D,F]		x		x					x						x			x
Blood Draw - PK and Anti-APL-2/ PEG Ab [D]				x					x						x			x
Vital Signs [D,G]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical Examination [H]			x													x		x
Urine Pregnancy Test [E,F]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
BCVA [I]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Slit Lamp Examination		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Dilated Indirect Ophthalmoscopy		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
IOP Measurement		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
SD-OCT [J]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Digital Color Fundus Photographs (DCFP) [J]			x												x			x
Fundus Fluorescein Angiograms (FFA) [J]			x												x			x
Study Eye Determination	x																	
Mandatory anti-VEGF injection	x		x															
Anti-VEGF injection (PRN)				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
APL-2 administration injection			x	x	x	x	x	x	x	x	x	x	x	x	x			
Post-Injection Assessment [K]			x	x	x	x	x	x	x	x	x	x	x	x	x			
Concomitant Medication/ Concomitant Ocular Procedures [L]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

FOOTNOTES:

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

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

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

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

E. At screening, serum pregnancy should be performed for Woman of Child Bearing Potential (WOCBP). If positive, subject is not eligible to continue in the study.

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

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

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

I. Perform assessments prior to dilating the eyes.

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

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

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