STATISTICAL ANALYSIS PLAN

A multicenter, open-label, safety and proof-of-concept study to assess safety, tolerability and efficacy of AR-1105 in subjects with macular edema due to retinal vein occlusion (RVO)

Sponsor: Aerie Pharmaceuticals, Inc.

Protocol Number: AR-1105-CS201

Author: [redacted]

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Statistical Analysis Plan Approval

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List of Abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
AR-1105	Aerie's Dexamethasone Intravitreal Implant Drug Delivery System
BCVA	Best Corrected Visual Acuity
BRVO	Branch Retinal Vein Occlusion
CI	Confidence Interval
CFT	Central Foveal Thickness
CRT	Central Retinal Thickness
CRVO	Central Retinal Vein Occlusion
CS	Clinically Significant
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
FA	Fluorescein Angiography
FP	3-Field Fundus Photography
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not Clinically Significant
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
RTF	Rich Text Format
RVO	Retinal Vein Occlusion
SAP	Statistical Analysis Plan
SD	Standard Deviation
SD-OCT	Spectral-Domain Ocular Coherence Tomography
SDC	Statistics & Data Corporation, Incorporated
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol AR-1105-CS201, Amendment 1 (Rev 01) dated 22-JAN-2019.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP they may be completed and will be identified in the clinical study report.

2. Study Objectives

The primary objective of the study is to evaluate the safety and tolerability of 2 formulations of AR-1105 in subjects with macular edema due to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

The secondary objectives are:

- To evaluate the effect of AR-1105 on best corrected visual acuity (BCVA) by early treatment of diabetic retinopathy study (ETDRS) methodology
- To evaluate the effect of AR-1105 on central retinal thickness (CRT) and subretinal fluid by spectral-domain ocular coherence tomography (SD-OCT)

2.1 Primary Variables

The primary variables are related to safety and include the following:

- Ocular and non-ocular treatment-emergent adverse events (TEAE)
- Slit lamp biomicroscopy
- Dilated indirect ophthalmoscopy measures
- Intraocular pressure (IOP), including change from baseline and the proportion of study eyes with an increase from baseline in IOP of 10 mmHg or more and the proportion of study eyes with IOP of 30 mmHg or more.
- Vital signs
- Safety laboratory data

2.2 Secondary Variables

The secondary variables are related to efficacy and include the following:

- BCVA by ETDRS method
- CRT as assessed by SD-OCT
- Area of non-perfustion and area of leakage as assessed by fluorescein angiography (FA) and 3-field fundus photography (FP)
- Percentage of subjects receiving rescue therapy overall

2.3 Exploratory Variables

There are no exploratory variables for this study.

2.4 Statistical Hypotheses

The statistical analysis of primary efficacy variable is conducted to gain information for future studies.

The percentage of study eyes gaining at least 15 letters in BCVA from baseline will be summarized using discrete summary statistics, including exact 90% and 95% confidence intervals (CIs) by treatment group. Treatment group comparisons will be completed using Fisher's exact test.

Treatment group comparisions based on the 90% and 95% CIs using the Farrington-Manning score test will be completed.

$$H_0: p_1 - p_2 = 0$$

$$H_1: p_1 - p_2 \neq 0$$

where H_0 denotes the null hypothesis, and H_1 denotes the alternate hypothesis; p's denote the proportion of eyes gaining at least 15 letters for each treatment.

3. Study Design and Procedures

3.1 General Study Design

Study visits will be referred to in all tables and listings as the planned study day corresponding to the visit to enable reviewers to understand the assessment timing without referring to the protocol visit schedule. Table 1 shows the scheduled study visits, their planned study day, and the acceptable visit window for each study visit.

Table 1. Scheduled Visits, Study Days, and Visit Windows

Scheduled Visit	Planned Study Day	Visit Window
Visit 1	[redacted]	N/A
Visit 2		N/A
Visit 3		± 2 Days
[redacted]		± 2 Days
Visit 4		± 3 Days
Visit 5		± 3 Days
Visit 6		± 3 Days
Visit 7		± 3 Days
Visit 8		± 3 Days
Visit 9		± 3 Days
Visit 10		± 3 Days
Visit 11		± 3 Days
Visit 12		± 3 Days

3.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided on Table 2.

Table 2. Schedule of Visits and Procedures.

Procedure	Screening[1]	Baseline/ Treatment	Initial Phase		Follow-Up Period[1] (Randomized Phase)						Implant Observation Period[2] (if required)		
	V1 [redacted] to -1	V2 [redacted]	V3[3] [redacted] (± 2 days)	V3b[3] [redacted] (± 2 days)	V4 [redacted] (± 3 days)	V5 [redacted] (± 3 days)	V6 [redacted] (± 3 days)	V7 [redacted] (± 3 days)	V8 [redacted] (± 3 days)	V9 [redacted] (± 3 days)	V10 [redacted] (± 3 days)	V11 [redacted] (± 3 days)	V12 [redacted] (± 3 days)
Informed consent review	X												
Demographics/ medical & ocular history[5]	X												
Concomitant medication query	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events query		X	X	X	X	X	X	X	X	X	X	X	X
BCVA – (ETDRS)	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit-lamp biomicroscopy	X	X	X	X	X	X	X	X	X	X	X	X	X
Gonioscopy*	X	X					X*			X*			
IOP check	X	X	X	X	X	X	X	X	X	X	X	X	X
Posterior segment OCT*	X	X			X*	X*	X*	X*	X*	X*	X*	X*	X*
Fluorescein Angiography	X	X					X			X			
3-Field fundus photography*	X	X					X*			X*	X*	X*	X*
Dilated fundus exam*	X	X	X	X	X	X	X*	X	X	X*	X[4]	X*	X*
Vitreous implant residual assessment*			X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests	X				X	X				X			
Pregnancy test	X									X			
Treatment[6]		X											

[1] Screening and post-implant treatment schedule applies to both Cohorts.

[2] Implant observation period should continue for any individual subject as long as residual implant is visible, or to [redacted] whichever comes first.

[3] [redacted]

[4] An interim database lock may be conducted when the first 20 subjects have completed their [redacted] visit.

[5] [redacted]

[6] [redacted]

* Assessments performed in study eye only at these visits.

4. Study Treatments

4.1 Method of Assigning Subjects to Treatment Groups

[redacted]

Providing none of the subjects experience any clinically-meaningful ocular adverse reactions (possibly) related to treatment with AR-1105 during the initial phase, the study will continue into the randomized phase. During the randomized phase of the study, subjects will be assigned in a 1:1 ratio to either AR-1105-CF1 or AR-1105-CF2.

5. Sample Size and Power Considerations

This study is not powered to detect a pre-stated efficacy signal, but rather will be used to inform the design and power for future studies. With a sample size of 20 evaluable subjects per treatment group, the study will have 95% confidence of ruling out adverse events (AE) with true incidence rates of 13.9% or higher within each treatment group. That is, with 20 subjects in a treatment group, if an AE of a specific type is not observed, then with 95% confidence, the true incidence rate of that AE is less than 13.9%.

6. Data Preparation

All reported study data will be recorded on the electronic case report forms (eCRF) supplied by Statistic & Data Corporation (SDC). Only the Principal Investigator and authorized study staff according to the Delegation of Responsibilities log are entitled to make entries in the eCRF.

After data are entered into the clinical study database, electronic edit checks and data review will be performed. All data validation specifications and procedures are detailed in the Data Validation Manual as a separate document. When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after data have been locked can only be made with the approval of the Sponsor and Trial Runners in consultation with SDC.

The final analyses outlined in this document will be carried out after the following have occurred:

- All data management requirements are met according to SDC standard operating procedures, including data entry, performance of edit and validation checks, documentation and resolution of data queries, and database lock with written authorization provided by appropriate SDC and Sponsor personnel.
- Protocol deviations have been identified and status defined (major/minor deviations).
- Analysis populations have been determined.

7. Analysis Populations

7.1 Safety

The safety population will include all subjects who received study medication. This population will be used to summarize safety variables and will summarize subjects as treated.

7.2 Intent-to-Treat

The intent-to-treat (ITT) population will include all subjects who received study medication. This population will be the primary population for efficacy analyses and will be used to summarize all efficacy variables and will summarize subjects as treated.

7.3 Per Protocol

The per protocol (PP) population is a subset of the ITT population, which will include those subjects who do not have major protocol violations likely to seriously affect the efficacy outcomes of the study. This population will be the secondary population for efficacy analyses and will be used to summarize a subset of efficacy variables as needed. If the PP and ITT populations are exactly the same, then additional efficacy analyses on the PP population will not be performed. The PP population will summarize subjects as treated.

8. General Statistical Considerations

8.1 Unit of Analysis

The unit of analysis in this study will be the study eye (see Protocol Section 4.2 for details on selection of study eye) for all efficacy, and study eye and subject for safety summaries. Additionally, non-ocular AEs and medical history (ocular and non-ocular) will be presented at the subject level. Fellow eye safety summaries will also be presented as appropriate.

8.2 Missing or Inconclusive Data Handling

8.2.1 Missing/Partial dates for AEs

Missing/Partial AE start dates will be imputed as follows. The original dates will be displayed in data listings and the impuated dates will be used in derivations only for study day and TEAEs.

- Dates with missing day only will be imputed as the 1st of the month unless the month and year are the same as the month and year of the first exposure to treatement, in which case the missing day will be imputed as the first exposure to treatement day.
- Dates with both day and month missing will be imputed as 1 Jan unless the year is same as the year of first exposure to treatement, in which case missing day and month will be imputed as the first exposure to treatement day and month.
- A completely missing date will be imputed as the first exposure to treatement unless the AE end date is on or before the first exposure to treatement, in which case the missing date will be impuated as 1 Jan of the same year as the end date.

Missing/Partial AE end dates will be imputed as follows:

- Dates with missing day only will be imputed as the last day of the month.
- Dates with both day and month missing will be imputed as 31 Dec.
- Complete missing dates will not be impuated.

8.2.2 MISSING/PARTIAL DATES FOR CONCOMITANT MEDICATIONS

Missing/Partial start dates for concomitant medications will be imputed as follows. The original dates will be displayed in data listings and the impuated dates will be used in derivations only for the differentiation of prior and/or concomitant medications.

- Dates with missing day only will be imputed as the 1st of the month unless the month and year are the same as the month and year of the first exposure to treatment, in which case the missing day will be imputed as the first exposure to treatment day.
- Dates with both day and month missing will be imputed as 1 Jan unless the year is same as the year of first exposture to treatment, in which case missing day and month will be imputed as the first exposure to treatment day and month.
- A completely missing date will be imputed as the first exposure to treatment unless the concomitant medication end date is on or before the first dose date of study medication, in which case the missing date will be impuated as 1 Jan of the same year as the end date.

Missing/Partial end dates for concomitant medications will be imputed as follows:

- Dates with missing day only will be imputed as the last day of the month unless the month and year are the same as month and year of the last exposure to treatment, in which case missing day will be imputed as the last exposture to treatment day.
- Dates with both day and month missing will be imputed as 31 Dec unless the the year is the same as the year of the last exposure to treatment, in which case missing day and month will be imputed as the last exposture to treatment day and month.

- Complete missing dates will not be imputed.

8.2.3 MISSING DATA IN EFFICACY ANALYSIS

Missing data in efficacy analysis will be handled as follows:

- Using last observation carried forward (LOCF)
- Imputing missing as failure
- Using observed data only

Details are specified in Section 13.1.

8.3 Definition of Baseline

Baseline is defined as the last non-missing measurement on or before the study treatment date. If the Baseline visit (i.e. Visit 2) is missing, use the non-missing measurement from Screening visit (i.e. Visit 1) unless there is an unscheduled visit after Screening visit and before Baseline visit. Measurements from unscheduled visit on the study treatment date can not be used as baseline without the knowledge of if the measurement is taken before or after treatment exposure.

8.4 Data Analysis Conventions

All data analyses will be performed by SDC. Statistical programming and analyses will be performed using SAS® Version 9.4 or higher. Output will be provided in rich text format (RTF) for tables and portable document format (PDF) for tables, listings, and figures using landscape orientation. All study data will be listed by treatment (and phase [initial vs randomized] for CF1), subject and visit (as applicable).

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values. Summaries for discrete variables will include number and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). Change from baseline will be calculated as follow-up visit minus baseline.

All statistical tests will be two-sided with a significance level of 0.05 ($\alpha = 0.05$) unless otherwise specified. Confidence intervals for differences between treatment groups will be two-sided at 90% and 95% confidence. All p-values will be rounded to four decimal places; p-values less than 0.0001 will be presented as "<0.0001"; p-values greater than 0.9999 will be presented as ">0.9999."

Unless otherwise specified, summaries will be presented by treatment group and, where appropriate, visit.

8.5 Adjustments for Multiplicity

No adjustments for multiplicity are planned.

9. Disposition of Subjects

The following disposition items will be summarized:

- The number of subjects who were screened, screen failed, and treated
- The number and percentage of subjects in each analysis population
- The number and percentage of subjects who completed the study
- The number and percentage of subjects who discontinued from the study and the reasons for premature discontinuation. COVID-19 related discontinuation will be identified.
- The number and percentage of subjects with any deviations, any major or minor deviations, any deviations related to COVID-19. Major or minor deviations will be assigned by the Sponosr. COVID-19 related deviations can be major or minor as assigned by the Sponsor.

All percentages will use the number of subjects treated as the denominator, overall and by treatment group, unless indicated otherwise.

In addition, subject disposition (for safety population and for screen failed subjects), protocol deviations, inclusion/exclusion criteria violations listings will be provided. A separate data listing for COVID-19 related protocol deviations will be provided.

10. Demographic and Pretreatment Variables

10.1 Demographic Variables

The demographic variables collected in this study include age, gender, race, and ethnicity. Subjects who record more than one race will be grouped into a single category denoted as multi-racial. Demographic variables will be summarized and listed.

Age (years) will be summarized, overall and by treatment, using continuous descriptive statistics. Age will also be categorized as follows: <65 years and ≥65 years. Age will be reported in years and calculated using the following formula:

$$\text{Age} = (\text{Informed Consent Date} - \text{Date of Birth}) / 365.25, \text{ truncated as an integer}$$

The number and percentage of subjects will be presented, overall and by treatment, for age category, gender, race, and ethnicity.

Subject listings will be provided for demographic variables and childbearing potential for female subjects.

11. Medical History and Concomitant Medications

11.1 Medical History

A medical history will be obtained at the Screening visit. Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1.

Medical history will be summarized using discrete summary statistics and presented by treatment group at the subject level by System Organ Class (SOC) and Preferred Term (PT) using the Safety population. Ocular and non-ocular medical history will be summarized separately. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once.

Listings of medical history will be generated separately for ocular and non-ocular data.

11.2 Prior and Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary (WHODrug Global B3, September 2018) and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name. If the ATC 4 classification is not provided, the next lowest classification that is provided in the coding dictionary will be used. The preferred name will be defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients (e.g., multivitamins), then the drug name will be summarized as the preferred name.

Concomitant medications are defined as those medications listed as having been taken (1) prior to initiation of study medication administration and continuing for any period of time following the first administration of study medication or (2) at any time following the first administration of study medication.

Prior and concomitant medications will be summarized for all subjects. Medications will be tabulated for each treatment group using frequencies and percentages. Subjects may have more than 1 medication per ATC text. At each level of subject summarization, a subject will be counted once if he/she reports 1 or more medications. Percentages will be based on the number of subjects in each treatment group. Listings of prior and concomitant medications will be generated for ocular and non-ocular data.

12. Implant Residual Assessment

Duration of implant visibility in days will be calculated as: (End Date - Date of Implant Injection) + 1, where the end date is defined as the latest date at which the implant is visible or date of implant injection for subjects whose implants are not visible at any of the follow up visits. Vitreous implant visualization will also be summaried at each visit by by treatment group using categorical statistics. A subject listing will be provided for vitreous implantresidual assessment.

13. Efficacy Analyses

The efficacy analyses will include the following:

- Percentage of subjects with ≥15-letter improvement compared to baseline BCVA (assessd by ETDRS) at Month 6.
- Change from baseline in CRT as assessed by SD-OCT at Months 1, 2, 3, 4, 5, and 6
- Change from baseline BCVA letter score at Months 1, 2, 3, 4, 5, and 6
- Percentage of subjects with a ≥10-letter improvement compared to baseline BCVA at Months 1, 2, 3, 4, 5, and 6
- Percentage of subjects with a ≥10-letter worsening compared to baseline BCVA at Months 1, 2, 3, 4, 5, and 6
- Percentage of subjects with a ≥15 letter improvement compared to baseline BCVA at Months 1, 2, 3, 4, 5 and 6
- Percentage of subjects with a ≥15 letter worsening compared to baseline BCVA at Months 1, 2, 3, 4, 5, and 6
- Percentage of subjects receiving rescue therapy overall

13.1 Primary Analysis

The percentage of study eyes gaining at least 15 letters in BCVA from baseline will be summarized using discrete summary statistics, including exact 90% and 95% CIs by phase and treatment group.

Treatment group comparisons for study eye will be completed using:

- Fisher's exact statistic:

  Example SAS codes: PROC FREQ Data=xx;

  Weight count / ZEROS;

  Tables aa*treatment / FISHER;

  Run;

  where aa indicates Yes/No whether at least 15 letters gained.
- Exact 90% and 95% CIs using the Farrington-Manning score statistic:

  Example SAS codes: PROC FREQ data=xx;

  tables = aa*treatment/ riskdiff(cl=fm);

  Weight Count ;

  Run;

  where aa indicates Yes/No whether at least 15 letters gained.

- Exact logistic regression will be utilized to determine treatment effect on the percentage of study eyes gaining at least 15 letters in BCVA from baseline after adjusting for baseline BCVA. Odds ratio and 95% CI will be presented.

  Example SAS codes: PROC LOGISTIC data=xxx descending ;
  (e.g., to model probability of at least 15 letters change in BCVA; y-variable="Y");
  Class treatment;
  Model xx = treatment baseline_BCVA;
  Exact treatment baseline_BCVA / estimate = both;
  Run;

These analyses will be used to determine differences in formulations and to assess whether there are differences in outcomes.

The efficacy summaries will be performed on the ITT population:

- using LOCF (for continuous variables);
- imputing missing as failure (for categorical variables); and
- using observed data only.

Subjects who receive rescue medication prior to the summarized visit will be imputed as failures for the summarized visits. No additional imputation methodologies will be performed in this early phase study.

The percentage of subjects gaining or losing at least 15 letters at other study visits and the percentage of subjects gaining or losing at least 10 letters at each study visit will be analyzed similarly.

Change from baseline in BCVA letters to each follow-up visit will be summarized using continuous summary statistics, including 90% and 95% CIs by treatment group.

Box plot of change from baseline in BCVA letter score by visit and treatment group for study eye will be presented. Separate box plot of change from baseline in BCVA letter score for study eye will be presented for subjects with improvement of 15 or more letters, 10 or more letters, and 5 or more letters.

A linear model with change from baseline BCVA letters for study eye only as the response, baseline BCVA letters as a covariate, and treatment group as a main effect will be fit to determine treatment group effect with separate models completed for each follow-up visit. These analyses will be used to determine differences in formulations and may be used to assess whether there are differences in outcomes between subjects' data pre- and post-interim to determine whether the data may be pooled. Subjects who receive rescue medication prior to the summarized visit will have their measure replaced with their last observation prior to receiving rescue medication. The least squares mean, standard error, and CI for each treatment group, and the difference between treatment groups will be presented for

study eye only. Additionally, analyses will be completed using individual two-sample t-tests and 90% and 95% Cis around the difference between treatment groups in mean BCVA and mean change from baseline BCVA for study eye only.

Median time (in months) to achieve a treatment response of ≥15 letters improvement from baseline in BCVA for study eye and median time (in months) to rescue therapy will be estimated using Kaplan-Meier methods with 90% and 95% CI, calculated using the method of Brookmeyer and Crowley (1982). The log rank statistic will be used to determine differences in time to achieve response between the two treatment groups to determine differences in formulations. Cox proportional hazards will also be used to analyze time to event, including baseline BCVA as a covariate. Results from unscheduled visits or early termination visits will be included in the time to event analysis.

For the event of achieving a treatment response of ≥15 letters improvement from baseline in BCVA for study eye, the starting date will be the date of first dose. Subjects receiving rescue medications prior to or on the same date as the achievement of improvement will be considered censored on the day of rescue medication receipt; subjects with neither rescue medications received nor improvement achieved will be considered censored on the last date known to be rescue medication free and improvement achievement free. For the event of receiving rescue therapy, the starting date for the time to event evaluation will be the date of first dose. Subjects who do not receive rescue therapy will be considered censored on the last date known to be event free.

Example SAS codes: PROC LIFETEST Data=xxx method=KM;

```
Strata treatment/test=logrank;
Time AVAL*CENSOR(0);
Run;
where CENSOR indicates censored subjects.
PROC PHREG Data = xxx;
Class Treatment (param=ref ref='CF2');
model AVAL*CENSOR(0) = baseline_BCVA Treatment/ties=exact;
run;
where CENSOR indicates censored subjects.
```

In all analyses, data from subject visits after receipt of rescue medication will be imputed using last observation prior to receiving rescue medication for continuous endpoints and will be imputed as failures for success/failure variables.

Additionally, a subset of the efficacy analyses will be performed by combining the initial phase subjects with the randomization phase subjects.

13.2 SD-OCT, FA and FP

CRT measured by Cirrus (Zeiss) or Spectralis (Heidelberg) instrument will be summarized at each visit, using continuous summary statistics including change from baseline. Comparison between treatment groups for CRT will be performed using the same approaches as specified for BCVA in section 13.1.

Two time to event analyses for CRT of study eye as specified below will be evaluated using the same statistical method for the event of achieving a treatment response of ≥15 letters improvement from baseline in BCVA in section 12.1. The starting date of the evaluation will be the date of first dose. Results from unscheduled visits or early termination visits will be included in the time to event analysis.

- Time to resolution of macular edema: defined as first time point at which CRT is less than or equal to 315 µm for study eye.
- Time to loss of resolution of macular edema among treatment responders (population for this analysis includes subjects who achieved resolution of macular edema except on the last day of measurement): defined as first time point at which CRT returns to greater than 315 µm from first achieving the resolution of macular edema.

For the event of resolution of macular edema, subjects receiving rescue medication prior to or on the same date as the achievement of resolution of macular edema will be censored on the day of their rescue medication receipt. Subjects with neither rescue medications received, nor resolution of macular edema will be considered censored on the last date known to be rescue medication free and resolution of macular edema free. For the event of loss of resolution of macular edema after resolution achieved, subjects receiving rescue medications prior to to the loss of resolution of macular edema will be considered censored on the day of rescue medication receipt and subjects receiving rescue medications on the same date as loss of macular edema will be considered for loss of macular edema. Subjects with neither loss of resolution of macular edema nor rescue medication received will be considered censored on the last date known to be loss of resolution of macular edema free and rescue medication free.

Total area of capillary non perfusion within ETDRS Grid (16DA) and total area of fluorescein leakage within the ETDRS grid assessed by FA using both Optos instruments (i.e ultra-widefield) and non-Optos (i.e widefield) will be summarized using continuous summary statistics.

Change in fluorescein leakage from Screening within the ETDRS Grid (16DA) assessed by FA will be summarized using discrete summary statistics including change from baseline.

Separate subject listings of SD-OCT and FA results will be produced.

Box plot of change from baseline in CRT for study eye only will be presented.

Line plot of CRT for study eye will be prepared with visit on x-axis and mean change from baseline in CRT withon y-axis by treatment group.

14. Exploratory Analyses

There are no exploratory analyses planned for this study.

15. Safety Analyses

All safety analyses will be conducted using the Safety population.

15.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug-related. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease occurring after informed consent form is signed and dated, without any judgment about causality. Any pre-existing medical condition that worsens after first administration of the study medication will also be considered a new AE. The AE reporting period starts from the time the subject signs and dates the informed consent and until 30 days after the subject's last study visit. All Aes will be coded using the MedDRA 21.1.

Treatment-emergent adverse events are defined as any event that occurs or worsens on or after the study treatment is initiated. Adverse events recorded in the eCRF which began prior to treatment will not be included in the summary tables but will be included in the AE data listings.

An overall summary will be presented that includes the number of TEAEs and the number and percentage of subjects who experienced at least one TEAE, by treatment group. This summary will also include breakdowns of TEAEs further categorized as ocular (study eye, fellow eye, and both eyes separately) or non-ocular, serious TEAEs, TEAEs by maximum severity, TEAEs by maximum relationship to study medication, TEAEs by maximum relationship to study procedure, TEAEs by maximum expectedness, number of serious TEAEs, number of subjects with any serious TEAEs, and with TEAEs leading to death.

Additional summaries of TEAEs will be provided showing the number and percentage of subjects who experienced at least one TEAE. These summaries will be presented by system organ class (SOC) and preferred term (PT). Non-ocular TEAEs will be summarized using discrete summary statistics and presented by treatment group at the subject level by SOC and PT. Ocular TEAEs will be similarly summarized at the subject level for study eyes, fellow eyes, and both eyes separately. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. In the summary, SOC will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all subjects within each SOC.

Separate summaries will be provided for the following categories of Aes:

- Ocular TEAEs in the study eye, fellow eye, both eyes

- Non-ocular TEAEs
- Ocular TEAEs related/possibly related to study medication
- Non-Ocular TEAEs related/possibly related to study medication
- Ocular TEAEs related/possibly related to study procedure
- Non-Ocular TEAEs related/possibly related to study procedure
- Serious TEAEs
- Serious TEAEs related/possibly related to study medication

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made irrespective of relationship to study medication or seriousness of the event and should be evaluated according to the following scale:

- *Mild:* Present and noticeable, but not distressing, and no disruption of normal daily activities.
- *Moderate:* Discomfort sufficient to possibly reduce or affect normal daily activity.
- *Severe*: Incapacitating, with inability to work or perform normal daily activity.

The relationship of each AE to the study medication should be determined by the Investigator using these explanations:

- *Not Related:* The event is clearly related to other factors such as subject's clinical condition, therapeutic interventions, concomitant disease, or therapy administered to the subject and does not follow a known response pattern to the product.
- *Unlikely Related:* The event is most probably caused by other etiologies such as participant's underlying condition, therapeutic intervention, or concomitant therapy, or the delay between administration and the onset of the AE is incompatible with a causal relationship. Therefore, there is not a reasonable possibility that the AE was caused by the study medication.
- *Possibly Related:* The event follows a reasonable, temporal sequence from the time of study medication administration and/or follows a known response pattern to the study medication, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant therapy administered to the subject.
- *Related:* The event follows a reasonable, temporal sequence from the time of study medication administration and/or follows a known response pattern to the study medication and cannot be reasonably explained by other factors such as subject's clinical state, therapeutic interventions, or concomitant therapy administered to the subject, and either occurs immediately following study

medication administration, or improves on stopping the study medication, or reappears on repeat exposure, or there is a positive reaction at the application site.

Summaries of TEAEs by maximum severity and by maximum relationship will be presented for ocular Aes and non-ocular Aes separately. The number of subjects with any TEAEs (along with percentages) will be tabulated by SOC and PT within each SOC by treatment group. To count the number of subjects with any TEAEs, if a subject has multiple TEAEs coded to the same PT within the same SOC, the subject will be counted once under the maximum severity or relationship..

Individual subject listing will be provide for all AEs, the AEs leading to death, serious AEs, COVID-19 related AEs, and COVID-19 related serious AEs.

15.2 Slit-Lamp Biomicroscopy Examination

A slit-lamp biomicroscopy examination of the cornea, conjunctiva, anterior chamber, lens, and lids will be performed at each visit. The results will be graded as clinically significant (CS) or not clinically significant (NCS).

The results will be summarized using the numbers and percentages for each treatment group and for all subjects at each visit for each eye (study eye and fellow eye). Percentages will be based on the numbers of subjects in each treatment group with responses. Shift tables for the slit-lamp biomicroscopy parameters will also be provided comparing each follow-up visit to the baseline. A subject listing of the slit-lamp biomicroscopy parameters will also be produced.

15.1 Dilated Ophthalmoscopy

A dilated ophthalmoscopy examination of the retina, macula, choroid, optic nerve, vitreous humour, and cup/disc ratio will be performed at each visit. Subject listings of dilated ophthalmoscopy results will be produced.

The results will be summarized using the numbers and percentages for each treatment group and for all subjects at each visit for each eye (study eye and fellow eye, if done at the visit). Percentages will be based on the numbers of subjects in each treatment group with responses. Shift tables for the dilated ophthalmoscopy parameters will also be provided comparing each follow-up visit to the baseline.

15.2 Intraocular Pressure

Intraocular pressure will be summarized at each visit, using continuous and discrete summary statistics, including change from baseline and the proportion of study eyes with an increase from baseline in IOP of 10 mmHg or more and the proportion of study eyes with IOP of 30 mmHg or more.

A subject listing of IOP will also be produced. Increase from baseline in IOP of 10 mmHg or more or IOP of 30 mmHg or more will be flagged in the listing.

15.3 Gonioscopy

Gonioscopy will be used to examine for anterior chamber angle abnormalites. A subject listing of gonioscopy results will be produced.

15.4 Vital Signs

Vital signs (heart rate, systolic sitting blood pressure, diastolic sitting blood pressure) data will be summarized at each visit, using continuous summary statistics, including change from baseline.

A subject listing of the vital signs results will also be produced.

15.5 Clinical Laboratory Data

The observed and change from baseline values of hematology and clinical chemistry parameters will be summarized, overall and by treatment group, at each visit with continuous descriptive statistics. Normal ranges will be used to determine the classifications. Values below the normal range will be classified as low normal, low panic, values above the normal range will be classified as high normal and high panic, and values within the normal range will be classified as normal. Analyses will also include shifts from baseline to each post-baseline visit using low normal, and high classifications.

Subject listings will be provided for hematology and clinical chemistry separately and will include a column to distinguish abnormal values.

16. Interim Analyses

An interim analysis may be conducted when the first 20 subjects enrolled in the randomized phase complete their Month 6 visit or discontinued the study. Safety, tolerability, and efficacy data will be reviewed during this interim analysis to assist in planning of future studies. A final analysis will be performed when all randomized subjects in each treatment group have completed the Month 6 visit.

17. Changes from Protocol-Stated Analyses

1. Comparison between treatment groups for CRT will be performed as specified in Section 12.2.
2. Two time to event analyses for CRT will be performed as specified in Section 12.2.
3. No analyses will be performed for CFT.
4. Discrete summary statistics for patient receiving rescue therapy will be removed.

18. References

Brookmeyer, R. and Crowley, J. (1982) A confidence interval for the median survival time. Biometrics 1982; 38: 29-41.

19. Revision History

Summary of Changes

Section #	Description of Change
List of Abbreviation	More abbreviation terms added
8.2.1	Missing/partial dates for AEs handling added
8.2.2	Missing/partial dates for concomitant medication handling added
8.3	Baseline definition updated
9	COVID-19 related discontinuation and protocol deviation added to subject disposition summary and COVID-19 related protocol deviation listing added
12	Implant residual assement added
13.1	1. Boxplot of change from baseline in BCVA letter score for study eye added for subject groups with gain of ≥15 letters, ≥10 letters, and ≥5 letters 2. More details for the event of receiving rescue therapy added
13.2	1. Comparison between treatment groups for CRT added 2. Line plot of mean change from baseline in CRT for study eye added 3. Time to resolution of macular edema and time loss of resolution of macular edema among treatment responders evaluation added 4. Details for FA assessment added
15.1	1. AE documentation starting and ending period clarified 2. AE overall summary table description revised 3. COVID-19 related AE and SAE listings added 4. AEs leading to early treatment discontinuation removed from subject disposition summary and listing
17	Changes from protocol stated analyses updated
19	Revision history updated
20	List of tables updated
21	List of listings updated
22	List of figures updated

20. Tables

Table Number	Title	Population
Table 14.1.1	**Subject Disposition**	**All Subjects**
Table 14.1.2.1	**Demographics**	**Safety Population**
Table 14.1.3.1	Ocular Medical History	Safety Population
Table 14.1.3.2	Non-Ocular Medical History	Safety Population
Table 14.1.4.1	Ocular Prior and Concomitant Medications	Safety Population
Table 14.1.4.2	Non-Ocular Prior and Concomitant Medications	Safety Population
Table 14.1.5	Implant Residual Assessment	Safety Population

Table 14.2.1.1.1	**Best Corrected Visual Acuity Letter Score (Month 6) – Categorical Summary**	**ITT Population (Missing Imputed as Failures)**
Table 14.2.1.1.2.1	Best Corrected Visual Acuity Letter Score (All Visits)– Categorical Summary (15-Letter or More Improvement)	ITT Population (Missing Imputed as Failures)
Table 14.2.1.1.2.2	Best Corrected Visual Acuity Letter Score (All Visits)– Categorical Summary (15-Letter or More Worsening)	ITT Population (Missing Imputed as Failures)
Table 14.2.1.1.2.3	Best Corrected Visual Acuity Letter Score (All Visits)– Categorical Summary (10-Letter or More Improvement)	ITT Population (Missing Imputed as Failures)
Table 14.2.1.1.2.4	Best Corrected Visual Acuity Letter Score (All Visits)– Categorical Summary (10-Letter or More Worsening)	ITT Population (Missing Imputed as Failures)
Table 14.2.1.1.3.1	Best Corrected Visual Acuity Letter Score (All Visits) – Categorical Summary (15-Letter or More Improvement)	ITT Population (Observed Case)
Table 14.2.1.1.3.2	Best Corrected Visual Acuity Letter Score (All Visits) – Categorical Summary (15-Letter or More Worsening)	ITT Population (Observed Case)
Table 14.2.1.1.3.3	Best Corrected Visual Acuity Letter Score (All Visits) – Categorical Summary (10-Letter or More Improvement)	ITT Population (Observed Case)
Table 14.2.1.1.3.4	Best Corrected Visual Acuity Letter Score (All Visits) – Categorical Summary (10-Letter or More Worsening)	ITT Population (Observed Case)
Table 14.2.1.2.1	Best Corrected Visual Acuity Letter Score - Continuous Summary	ITT Population (LOCF)
Table 14.2.1.2.2	Best Corrected Visual Acuity Letter Score – Continuous Summary	ITT Population (Observed Case)
Table 14.2.1.3	Time to Achievement of 15 Letters or More Improvement from Baseline in BCVA	ITT Population
Table 14.2.2.1.1	**Spectral-Domain Optical Coherence Tomography (SD-OCT) Central Retinal Thickness (CRT)**	**ITT Population (LOCF)**
Table 14.2.2.1.2	Spectral-Domain Optical Coherence Tomography (SD-OCT) Central Retinal Thickness (CRT)	ITT Population (Observed Case)
Table 14.2.2.2.1	Total Area of Capillary Non-perfusion and Total Area of Fluorescein Leakage within the ETDRS Grid (16DA) Assessed by FA and FP	ITT Population (Observed Case)
Table 14.2.2.2.2	Change in Flurescein Leakage from Screening within the ETDRS Grid (16DA) Assessed by FA and FP	ITT Population
Table 14.2.2.3.1	Time to Resolution of Macular Edema ITT Population	ITT Population
Table 14.2.2.3.2	Time to Loss of Resolution of Macular Edema Among Treatment Responders ITT Population	ITT Population
Table 14.2.3	Time to Administration of Rescue Treatment	ITT Population

Table 14.3.1	Overall Summary of Treatment-Emergent Adverse Events by Treatment Group	Safety Population
Table 14.3.2	Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.3	Non-Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.4	Ocular Treatment-Emergent Adverse Events Related/Possibly Related to Study Medication by System Organ Class and Preferred Term	Safety Population
Table 14.3.5	Non-Ocular Treatment-Emergent Adverse Events Related/Possibly Related to Study Medication by System Organ Class and Preferred Term	Safety Population
Table 14.3.6	Ocular Treatment-Emergent Adverse Events Related/Possibly Related to Study Procedure by System Organ Class and Preferred Term	Safety Population
Table 14.3.7	Non-Ocular Treatment-Emergent Adverse Events Related/Possibly Related to Study Procedure by System Organ Class and Preferred Term	Safety Population
Table 14.3.8	Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.9	Serious Treatment-Emergent Adverse Events Related/Possibly Related to Study Medication by System Organ Class and Preferred Term	Safety Population
Table 14.3.10	Ocular Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Medication Relationship	Safety Population
Table 14.3.11	Non-Ocular Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Medication Relationship	Safety Population
Table 14.3.12	Ocular Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity	Safety Population
Table 14.3.13	Non-Ocular Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity	Safety Population
Table 14.3.14.1	Hematology Results by Treatment Group and Visit	Safety Population
Table 14.3.14.2	Hematology Shifts from Baseline	Safety Population
Table 14.3.15.1	Chemistry Results by Group and Visit	Safety Population
Table 14.3.15.2	Chemistry Shifts from Baseline	Safety Population
Table 14.3.16.1	Slit-Lamp Biomicroscopy	Safety Population
Table 14.3.16.2	Slit-Lamp Biomicroscopy – Shift Table	Safety Population

Table 14.3.17.1	Dilated Ophthalmoscopy	Safety Population
Table 14.3.17.2	Dilated Ophthalmoscopy – Shift Table	Safety Population
Table 14.3.18	Intraocular Pressure (IOP)	Safety Population
Table 14.3.19	Vital Signs	Safety Population

21. Listings

Listing Number	Title	Population
Listing 16.1.7	Randomization Schedule	Safety Population
Listing 16.2.1.1	Subject Disposition	Safety Population
Listing 16.2.1.2	Subject Disposition	Screen Failed Subjects
Listing 16.2.1.3	Inclusion/Exclusion Criteria Violations	Safety Population
Listing 16.2.2.1	Protocol Deviations	Safety Population
Listing 16.2.2.2	COVID-19 Related Protocol Deviations	Safety Population
Listing 16.2.3	Analysis Populations	
Listing 16.2.4.1	Demographics	Safety Population
Listing 16.2.4.2	Childbearing Potential of Female Subjects	Safety Population
Listing 16.2.4.3	Ocular Medical History	Safety Population
Listing 16.2.4.4	Non-Ocular Medical History	Safety Population
Listing 16.2.4.5	Prior and Concomitant Medications	Safety Population
Listing 16.2.5.1	Intravitreal Injection	Safety Population
Listing 16.2.5.2	Implant Assessment	Safety Population
Listing 16.2.5.3	Study Drug Assignment	Safety Population
Listing 16.2.6.1	Best Corrected Visual Acuity (ETDRS)	Safety Population
Listing 16.2.6.2.1	Spectral - Domain Optical Coherence Tomography (SD-OCT)	Safety Population
Listing 16.2.6.2.2	Fluorescein Angiography (FA)	Safety Population

Listing 16.2.7.1	All Adverse Events	Safety Population
Listing 16.2.7.2	Serious Adverse Events	Safety Population
Listing 16.2.7.3	Adverse Events Leading to Death	Safety Population
Listing 16.2.7.4	COVID-19 Related Adverse Events	Safety Population
Listing 16.2.7.5	COVID-19 Related Serious Adverse Events	Safety Population
Listing 16.2.8.1	Hematology Results	Safety Population
Listing 16.2.8.2	Chemistry Results	Safety Population
Listing 16.2.8.3	Slit-Lamp Biomicroscopy Examination	Safety Population
Listing 16.2.8.4	Dilated Ophthalmoscopy	Safety Population
Listing 16.2.8.5	Intraocular Pressure (IOP)	Safety Population
Listing 16.2.8.6	Vital Signs	Safety Population
Listing 16.2.8.7	Pregnancy Test	Safety Population (Female Subjects)
Listing 16.2.8.8	Gonioscopy	Safety Population

22. Figures

Figure Number	Title	Population
Figure 14.2.1.1	Box Plot of Change from Baseline in BCVA Letter Score (Study Eye)	ITT Population
Figure 14.2.1.2	Box Plot of Change from Baseline in BCVA Letter Score (Study Eye) Categories of Improvement (≥5, ≥10, ≥15 Letters)	ITT Population
Figure 14.2.2	Box Plot of Change from Baseline in Central Retinal Thickness (CRT) Assessed by SD-OCT (Study Eye)	ITT Population
Figure 14.2.3	Line Plot of Mean Change from Baseline in Central Retinal (CRT) Assessed by SD-OCT (Study Eye)	ITT Population