16.1.9 Documentation of Statistical Methods
16.1.9.1 Statistical Analysis Plan

Statistical Analysis Plan Version	Statistical Analysis Plan Date
Version 1.0	19 Oct 2022

Statistical Analysis Plan (SAP)

Protocol Title:	An Open Label, Two-Arm Study in Subjects with Chorioretinal Vascular Disease to Evaluate ABP 938 and Aflibercept (Eylea®) in a Prefilled Syringe
Protocol Number:	20210034
Protocol Version, Date	Version 1.0, 19 Oct 2022
ICON ID:	0302/2363
Document Version, Date:	Version 1.0, 17 Jan 2022

Prepared by:

ICON Clinical Research Services

On behalf of:

Amgen Inc.

One Amgen Center Drive

Thousand Oaks, CA 91320-1799

NCT number: NCT05704725
This NCT number has been applied to the document
for purposes of posting on clinicaltrials.gov

Statistical Analysis Plan (SAP)

Statistical Analysis Plan (SAP)

SIGNATURE PAGE

P ared at ICON Clinical Research by:

[redacted] 18 Jan 2023 18:09:58 UTC (Z)

REASON: I approve this document

a6abd90c-91c0-41ae-aac1-8456384a198d

[redacted], Senior Biostatistician

18-JAN-2023

Date (DD Mmm YYYY)

Reviewed at ICON Clinical Research by:

[redacted] 18 Jan 2023 18:39:32 UTC (Z)

REASON: I approve this document

71c58482-18a9-4a72-9c38-4eb08379d037

[redacted], Senior Biostatistician

01/18/2023

Date (DD Mmm YYYY)

Approved at Amgen, Inc. **by:**

[redacted] 18 Jan 2023 16:55:52 UTC (Z)

REASON: I approve this document

22bb4740-0153-4f5c-bc16-bdce65c2f77c

[redacted], Senior Manager, Biostatistics, Biosimilars

01/18/2023

Date (DD Mmm YYYY)

Statistical Analysis Plan (SAP)

[redacted] 18 Jan 2023 17:11:42 UTC (Z)

REASON: I approve this document

826fd546-1d0c-45b2-a29e-f7bba6b52b22

18Jan2023

[redacted] MD, PhD, Global Development Lead, Biosimilars

Date (DD Mmm YYYY)

DocUUID : e2994b29-81b1-4ff9-ab3b-fe25a6ed0615

Statistical Analysis Plan (SAP)

REVISION HISTORY

Version/Date	Version name	Section	Changes implemented
Version 1.0/ 17-JAN-2023	20210034-SAP-Final_V1.0_17-JAN-2023	N/A	N/A

Statistical Analysis Plan (SAP)

TABLE OF CONTENTS

Statistical Analysis Plan (SAP)

DocUUID : e2994b29-81b1-4ff9-ab3b-fe25a6ed0615

Statistical Analysis Plan (SAP)

LIST OF ABBREVIATIONS

The following abbreviations will be used within this Statistical Analysis Plan (SAP).

Abbreviation or special term	Explanation
AE	Adverse Event
AMD	Age-Related Macular Degeneration
BCVA	Best Corrected Visual Acuity
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CTMS	Clinical Trials Management System
CVD	Chorioretinal Vascular Disease
DBL	Database Lock
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
eCRF	Electronic Case Report Form
EOI	Events of Interest
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IOP	Intraocular Pressure
IP	Investigational Product
IRT	Interactive Response Technology
IVT	Intravitreal
IXRS	Interactive Voice/Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
PD	Protocol Deviations
PFS	Prefilled Syringe
PT	Preferred Term
RVO	Retinal Vein Occlusion
Q1	Lower Quartile
Q3	Upper Quartile

DocUUID : e2994b29-81b1-4ff9-ab3b-fe25a6ed0615

Statistical Analysis Plan (SAP)

SAE	Serious Adverse Event
SAS	Statistical Analysis System
SAP	Statistical Analysis Plan
SD	Standard Deviation
SD-OCT	Spectral Domain-Optical Coherence Tomography
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
TE-SAE	Treatment-Emergent Serious Adverse Events
TFLs	Tables, Figures and Listings

Statistical Analysis Plan (SAP)

1 INTRODUCTION

The purpose of this SAP is to provide detailed descriptions of the statistical methods, data derivations and data displays for the final analysis for study protocol 20210034 "An Open Label, Two-Arm Study in Subjects with Chorioretinal Vascular Disease to Evaluate ABP 938 and Aflibercept (Eylea®) in a Prefilled Syringe" dated 19 Oct 2022. The table of contents and templates for the Table, Figures, Listings (TFLs) will be produced in a separate document.

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

The preparation of this SAP has been based on International Conference on Harmonization (ICH) E9 and E3 guidelines. This SAP will be finalized prior to first patient randomized to maintain trial integrity in accordance with ICON standard operating procedures (SOP). SAP amendments will not be permitted after the first subject has been randomized.

All data analyses and generation of TFLs will be performed using Statistical Analysis System (SAS) 9.4® or higher.

Statistical Analysis Plan (SAP)

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objective for this study is to assess the ability of retina specialists to successfully administer, via an intravitreal (IVT) injection, a 2 mg dose of ABP 938, using the ABP 938 Prefilled Syringe (PFS), compared to a 2 mg dose of aflibercept using the aflibercept PFS.

2.2 Secondary Objective(s)

The secondary objective is to assess the safety of ABP 938 administered to subjects with Chorioretinal Vascular Disease (CVD) via an IVT injection, using the ABP 938 PFS compared to aflibercept administered using the aflibercept PFS.

3 STUDY DESIGN

3.1 General Study Design

This is an open label, two-arm, randomized, multi-site study within the US in adult subjects with CVD. Approximately 48 adult male or female subjects will be randomized in a ratio of 2:1 to receive either a single IVT injection of ABP 938 in a PFS or a single injection of aflibercept in a PFS. Randomization will be stratified by retina specialist.

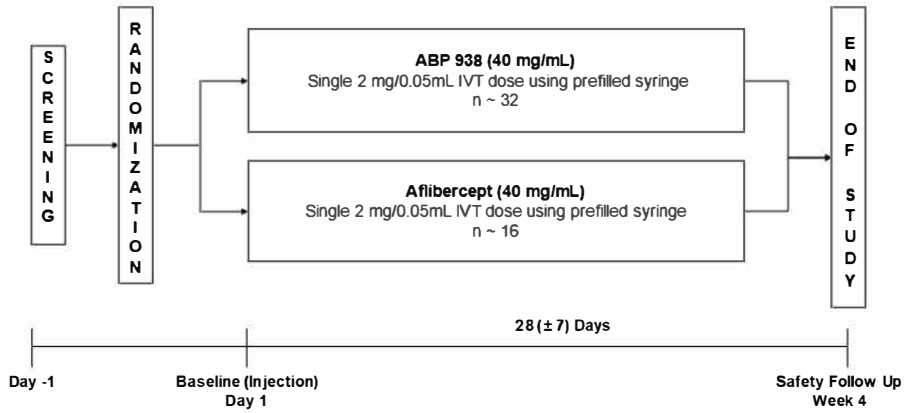
The study population will include men or women with treatment-naïve or previously treated neovascular Age-Related Macular Degeneration (AMD), Diabetic Macular Edema (DME), macular edema following Retinal Vein Occlusion (RVO), or Diabetic Retinopathy (DR), in whom treatment with aflibercept is indicated.

The study duration for each subject will be approximately 28 days (± 7 days) excluding screening and the study will end for subjects when they complete the end of study visit assessments.

The study design is outlined in Figure 1, and the visit schedule and planned assessments at each visit are detailed in Table 1.

No interim analyses are planned.

Figure 1: Study Flow Chart



IVT = intravitreal; mg = milligram; mL = milliliter; n = number of subjects.

3.2 Study Eye

Only one eye is selected as the study eye by retina specialists. The study eye selection recorded in the eCRFs will be used for all statistical analyses.

3.3 Randomization and Masking

Randomization will be performed through a centralized IXRS. On Day 1, eligible subjects will be assigned to ABP 938 or aflibercept in a 2:1 ratio. Each subject will receive a unique randomization number when he/she is assigned treatment. Subjects will be allocated to treatment according to the randomization code. Randomization will be stratified by retina specialist.

Investigators, site staff, and study teams will not be masked to treatment assignments. However, final live randomization lists will not be released to study teams until the database has been locked and approval of release is obtained from the Sponsor by ICON. Additionally, dry run statistical outputs generated prior to database lock in preparation for final analysis will be restricted to the ICON and Amgen statistical and programming teams.

3.4 Study Treatments and Assessments

The study consists of a screening visit (Day -1), a baseline visit (Day 1) and an end of study visit (Day 28 ± 7 days).

At the screening visit (Day -1), the investigator will obtain signed informed consent from the subject before any study procedures or assessments are performed. Once subject eligibility is confirmed the subject will be enrolled into the study. At this visit, the subject will undergo ocular safety procedures including the Best Corrected Visual Acuity (BCVA) scale, intraocular pressure (IOP), slit-lamp biomicroscopy, indirect ophthalmoscopy, and spectral domain-optical coherence tomography (SD-OCT).

At the baseline visit (Day 1), the subject will be randomized to receive a single IVT injection of either ABP 938 or aflibercept (open label) in a PFS administered by a retina specialist. Only one eye will be selected as the study eye. IOP will be measured, and indirect ophthalmoscopy will be performed before and after investigational product (IP) administration. The screening and baseline visit may be combined into one visit (Day 1).

At the end of study visit (Day 28 ± 7 days), the ocular safety procedures performed at the screening visit will be repeated.

Adverse events (AEs) will be collected from the signing of the informed consent form (ICF) until the end of study visit.

The method of assigning subjects to treatment is discussed in section 3.3 of this SAP.

A detailed description of procedures and assessments to be conducted during this study is summarized in the Scheduled of Study Assessments in Table 1 below.

Table 1: Schedule of Assessments

Study Procedure	Screening	Baseline (Randomization and Injection)	End of Study[b] (± 7 days)
	Day -1	Day 1[a]	Day 28
Informed Consent	X		
Medical and Ophthalmic History	X		
Demographic Data	X		
Concomitant Medications	X	X	X
Adverse Events [c]	X	X	X
BCVA by ETDRS [d]	X		X
Slit-Lamp Biomicroscopy [d]	X		X
Intraocular Pressure (IOP) [d]	X	X [e]	X
Indirect Ophthalmoscopy [d]	X	X [f]	X
SD-OCT [d]	X		X
Urine Pregnancy [g]	X		
Randomization		X	
IVT Injection of Study Medication (ABP 938 or aflibercept)		X	

BCVA = Best Corrected Visual Acuity; ETDRS = Early Treatment Diabetic Retinopathy Study;
IVT = Intravitreal; IOP = Intraocular pressure; SD-OCT = Spectral Domain-Optical Coherence Tomography

[a] The screening and baseline visits may be combined on Day 1.

[b] In the event of premature discontinuation, the subject should complete the assessments indicated at the end of study visit, whenever possible.

[c] Adverse events will be collected from the signing of the informed consent form until the end of study visit.

[d] All ophthalmic safety assessments should be performed on the study eye only.

[e] IOP will be measured pre-dose (prior to dilation) and 15-60 minutes after IP administration.

[f] Indirect ophthalmoscopy will be performed pre-dose and after IP administration.

[g] Required for females of childbearing potential. Test will be performed by local laboratory.

4 STUDY ENDPOINTS

4.1 Primary Endpoint(s)

The primary endpoint for the study is the proportion of IVT injections successfully administered to subjects with CVD by retina specialists, utilizing the ABP 938 PFS or aflibercept PFS.

4.2 Secondary Endpoint(s)

The secondary endpoint for the study is the incidence of ocular AEs and serious adverse events (SAEs) in the study eye, and non-ocular SAEs until the end of study visit (Day 28 visit).

Statistical Analysis Plan (SAP)

5 SAMPLE SIZE AND POWER

For this study, no prospective calculations of statistical power have been made.

It is planned to enroll approximately 48 adult male or female subjects into the study, with a minimum of 32 subjects in the ABP 938 PFS arm and a minimum of 16 subjects in the aflibercept PFS arm, randomized in a ratio of 2:1.

Statistical Analysis Plan (SAP)

6 ANALYSIS POPULATIONS

6.1 Full Analysis Set (FAS)

The FAS will include all randomized subjects and will be analyzed according to randomized treatment. This analysis set will be used for summaries of the primary endpoint.

6.2 Safety Analysis Set

The Safety Analysis Set will include all randomized subjects who receive the IP and will be analyzed according to the actual treatment received. This analysis set will be used for summaries of safety data.

6.3 Protocol Deviations/Violations and Exclusions from Analysis Sets

Protocol deviations will be collected and recorded during the trial. However, important protocol deviations will not be a cause for subject exclusion from any analysis sets. Protocol deviations will be summarized in accordance with section 8.3 of this SAP.

7 STATISTICAL CONSIDERATIONS AND ANALYSIS

7.1 Derived Variables

The below table provides the list of derived variables for demographic and baseline characteristics, duration derivations, and baseline derivations applicable for this study.

Table 2: Derived Variables

Variables	Formula
Derivation of Duration	
Study day at any visit	Date of interest – date of first dose of study drug. One day is added if this difference is ≥ 0
Baseline Derivations	
Baseline	The baseline value is defined as the last non-missing measurement before IP administration
Change from baseline	Post-baseline value – Baseline value

7.2 Handling of Missing Data and Outliers

Missing data will not be imputed for the primary and secondary endpoints with the exception of missing or incomplete dates as specified in section 7.2.2.

7.2.1 Missing Data Analysis Methods

All analyses will be carried out with observed data only.

7.2.2 Handling of Missing or Incomplete Dates

If dates are missing or incomplete for an AE (including deaths) or concomitant medication, the following algorithm will be used for imputation:

Table 3: Imputation Rules for Partial or Missing Start Dates

Start Date		Stop Date: Complete: *yyyymmdd* <1st dose	Complete: *yyyymmdd* ≥1st dose	Partial: *yyyymm* <1st dose *yyyymm*	Partial: *yyyymm* ≥1st dose *yyyymm*	Partial: *yyyy* <1st dose *yyyy*	Partial: *yyyy* ≥1st dose *yyyy*	missing
Partial: *yyyymm*	= 1st dose *yyyymm*	2	1	n/a	1	n/a	1	1
	≠ 1st dose *yyyymm*		2	2	2	2	2	2
Partial: *yyyy*	= 1st dose *yyyy*	3	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute as the date of first dose
2 = Impute as the first of the month
3 = Impute as January 1 of the year
4 = Impute as January 1 of the stop year

Note: If the start date imputation leads to a start date that is after the stop date, then there is a data error and do not impute the start date.

Imputation rules for partial or missing stop dates:

1. Initial imputation
    a. For partial stop date "mmyyyy", impute the last of the month.
    b. For partial stop date "yyyy", impute December 31 of the year.
    c. For completely missing stop date, do not impute.
2. If the stop date imputation leads to a stop date that is after the death date, then impute the stop date as the death date.
3. If the stop date imputation leads to a stop date that is before the start date, then there is a data error and do not impute the stop date.

Imputation rules for partial or missing death dates:

4. If death year and month are available but day is missing:
    a. If "mmyyyy" for last contact date = "mmyyyy" for death date, set death date to the day after the last contact date.
    b. If "mmyyyy" for last contact date < "mmyyyy" for death date, set death date to the first day of the death month.
    c. If "mmyyyy" for last contact date > "mmyyyy" for death date, data error and do not impute.
5. If both month and day are missing for death date or a death date is totally missing, set death

Statistical Analysis Plan (SAP)

date to the day after the last contact date.

The imputed dates will be used to assess whether AEs should be considered as treatment-emergent and if medications should be included in the safety summaries as prior or concomitant, however the original, partial dates will be included in data listings.

Statistical Analysis Plan (SAP)

8 STATISTICAL METHODS

8.1 General Statistical Conventions

Continuous variables will be summarized using descriptive statistics, including number of subjects (n), mean, median, standard deviation (SD), first and third quartiles, minimum and maximum.

For categorical variables, summaries will include counts of subjects and percentages. Percentages will be rounded to one decimal place.

Two-sided 95% confidence intervals (CI) will be provided when relevant.

For summary purposes, all summaries will be presented by treatment group unless otherwise specified.

8.2 Disposition

8.2.1 Summary of Study Reporting Period

A summary of key dates for the study will be reported including:

- First subject enrollment
- Last subject enrollment
- Last subject end of IP
- Last subject end of study
- Data cut-off date

8.2.2 Subject Disposition

Subject disposition information will be summarized by treatment group and for all subjects. The number of subjects and percentage of subjects who were randomized, who were dosed, who completed the study and who discontinued from the study will be presented. The primary reason for study discontinuation will also be tabulated. COVID-19 related discontinuations will be summarized as well. Separate summaries will be generated using the FAS and Safety Analysis Set.

A listing of discontinued subjects will be produced.

8.2.3 Summary of Analysis Sets

A separate summary of analysis sets will be produced using all screened subjects. The number of total screened subjects and randomized subjects by treatment group and overall will be summarized. Additionally, the number and percentage of subjects in each analysis set (FAS and Safety Analysis Set) will also be tabulated. The number and percentage of subjects excluded from each analysis set will be presented with the reasons for exclusion.

8.3 Protocol Deviations

Protocol deviations (PD) data will be entered into the Clinical Trials Management System (CTMS). The study team will conduct reviews of the PD data from CTMS. All PDs will be categorized as important or not important prior to the database lock and release of final live randomization lists.

Based on the PD data entered CTMS, a summary of important PDs will be tabulated using number and percentage of subjects with important PDs by category and deviation type, by randomized treatment group and for all subjects using the FAS. A summary table of COVID related PDs will also be tabulated in a similar manner. Subject listings of subjects with important PDs and COVID-19 related PDs will be provided.

8.4 Demographics, Baseline Characteristics, and Randomization Stratification

8.4.1 Demographics and Baseline Disease Characteristics

Age at baseline will be summarized using continuous descriptive statistics. Race, ethnicity, and sex, will be summarized using categorical descriptive statistics.

Any subjects that select more than one race will be summarized as "Multiple". The multiple racial combinations selected will be summarized under this "Multiple" category.

Baseline variables of BCVA, IOP, and SD-OCT will be summarized by descriptive statistics in the same way as continuous demographic variables.

Separate summaries will be generated for the FAS and Safety Analysis Set.

8.4.2 Summary of Randomization Stratification

The count and percentage of subjects randomized under each retina specialist (randomization stratum) will be summarized using the FAS population. Subjects randomized under the incorrect retina specialist will be summarized as well.

8.4.3 Medical History

Summaries of unresolved medical history will be presented by system organ class (SOC) and preferred term (PT) using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) at the time of the final analysis by treatment group and overall using FAS population.

8.4.4 Prior and Concomitant Medications

Medications used in this study will be coded by using the current version of the World Health Organization Drug Dictionary at the time of the final analysis.

Prior medications: are defined as those that were stopped at or within 30 days prior to the baseline visit.

Concomitant medications: are defined as those that are ongoing at the time of IP administration and

during the follow-up period.

Ocular study eye, ocular fellow eye, and non-ocular concomitant medications will be summarized descriptively using frequency tables by preferred name by treatment group and overall using the Safety Analysis Set.

Details for imputing missing or partial start and/or stop dates of medication are described in section 7.2.2.

8.5 Primary Endpoint Analysis

8.5.1 Analysis Methods

8.5.1.1 Multiplicity

No formal statistical hypothesis testing will be conducted as part of this SAP. As such, type I error control will be not applicable.

8.5.1.2 Treatment by center interaction analysis (multi-center study)

Treatment by center interaction analyses will not be conducted as part of this SAP.

8.5.2 Analysis of Primary Endpoint(s)

The primary endpoint of the number of successful IP injections with the PFS will be summarized using the FAS with observed data only. Successful injections for the purpose of the analysis of the primary endpoint will be defined by the following response recorded by the retina specialists in the Investigational Product Administration eCRF for each subject:

Did the prefilled syringe allow as a safe and effective administration of the prescribed dose? (Yes/No)

The number and percentage of injections successfully administered utilizing the PFS will be provided descriptively by randomized treatment group. For each retina specialist, the number and percentage of successful IP injections will be summarized. The estimated success rate for each treatment group will be calculated by the average of each retina specialists' individual success rate. The variance of this estimator will be calculated as:

$$Var(p) = \frac{\sum_{i=1}^{K}(p_i - \bar{p})^2}{K(K-1)}$$

where p_i is the proportion of successful IVT injections administered for the i-th retina specialist and $\bar{p}$ is the average of proportions of successfully administered IVT injections across all retina specialists, K is the total number of retina specialists. T-distribution with (K - 1) degrees of freedom will be used to calculate the corresponding two-sided 95% CI.

Should any treatment group have 100% successful IP injections, then exact Clopper-Pearson 95% CIs will be presented for both treatment groups instead of CIs based on the t-distribution.

8.6 Secondary Endpoint(s) Analyses

The secondary endpoints of ocular AEs in the study eye, SAEs in the study eye and non-ocular SAEs will be summarized as described in section 8.7.1 using the Safety Analysis Set.

8.7 Safety Analyses

Safety analyses will be conducted on the Safety Analysis Set according to actual treatment received and will be performed for all safety variables specified below.

8.7.1 Adverse Events

Only TEAEs will be summarized. TEAEs are any AE with onset after IP administration. AEs that occur on the day of IP dosing will be categorized as TEAEs if the event is indicated as not starting before first dose of IP per recorded responses in the Adverse Event eCRF.

All AEs will be classified by Primary SOC and PT according to the most current version of MedDRA. The severity of each TEAE will be graded per Common Terminology Criteria for Adverse Events (CTCAE) v5.0 criteria.

In summaries by SOC and PT, TEAEs will be sorted by decreasing frequency by SOC and PTs within each SOC according to ABP 938. In summaries by PT, TEAEs will be sorted by decreasing frequency according to ABP 938.

Counting of TEAEs will be by subject, and subjects will be counted only once within each SOC or PT. For tables categorized by severity, subjects with multiple events within a SOC or PT will be counted under the category of their most severe event within that SOC or PT.

Details for imputing missing or partial start dates of AEs are described in section 7.2.2 of this SAP.

An overall summary table of TEAEs will be presented which will include the number and percentage of subjects with at least one of the following events:

- ocular TEAEs in the study eye,
- non-ocular TEAEs,
- ocular TE-SAEs in the study eye,
- non-ocular TE-SAEs,
- CTCAE grade >= 3 TEAEs,
- fatal TEAEs,
- COVID-19 TEAEs,
- TEAEs leading to discontinuation of study,
- IP related TEAEs,
- study procedure related TEAEs,
- device related TEAEs, and

DocUUID : e2994b29-81b1-4ff9-ab3b-fe25a6ed0615

- treatment-emergent Events of Interest (EOIs).

The EOIs to be summarized are as defined in Appendix 1 – Events of Interest.

Separate AE summary tables will include the following:

- Ocular TEAEs in the Study Eye by PT
- Non-Ocular TEAEs by PT
- Ocular TE-SAEs in the Study Eye by PT
- Non-Ocular TE-SAEs by PT
- Ocular TEAEs in the Study Eye by SOC, PT, and Maximum CTCAE Grade
- Non-Ocular TEAEs by SOC, PT, and Maximum CTCAE Grade
- Treatment-Emergent Intraocular Inflammation AEs by PT
- Treatment-Emergent Vitreous Haemorrhage AEs by PT
- TE-SAEs Occurring on or After Presumed Start Date of COVID-19 Infection by PT
- Treatment-Emergent COVID-19 AEs by PT
- Overall Summary of Treatment-Emergent EOIs
- Treatment-Emergent Endophthalmitis Events by PT
- Treatment-Emergent Increase in Intraocular Pressure Events by PT
- Treatment-Emergent Retinal Detachment Events by PT
- Treatment-Emergent Thromboembolic Events by PT
- TEAEs Resulting in Study Discontinuation by PT

The TEAEs of Intraocular Inflammation and Vitreous Haemorrhage are as defined in Appendix 2.

Subject listings of TE-SAEs and TE-SAEs occurring on or after positive COVID-19 infection in subjects diagnosed with COVID-19 will be generated.

8.7.2 Intraocular Pressure

Visit values and changes from baseline for IOP (mm Hg) will be summarized by actual treatment group at each visit and time point scheduled during treatment period using continuous descriptive statistics. Only the study eye will be summarized.

8.7.3 Slit-lamp Biomicroscopy

Visit values for slit-lamp biomicroscopy will be summarized by each region assessed and by actual treatment group at each visit and time point scheduled during treatment period using categorical descriptive statistics. Only the study eye will be summarized.

Separate summaries will be generated for shifts from baseline to the end of study visit using the study eye only.

DocUUID : e2994b29-81b1-4ff9-ab3b-fe25a6ed0615

Statistical Analysis Plan (SAP)

8.7.4 Indirect Ophthalmoscopy

Visit values for indirect ophthalmoscopy will be summarized by each region assessed and by actual treatment group at each visit and time point scheduled during treatment period using categorical descriptive statistics. Only the study eye will be summarized.

Separate summaries will be generated for shifts from baseline to each post-baseline assessment using the study eye only.

8.8 Other Endpoints

Other endpoints will be summarized using the FAS.

8.8.1 Best Corrected Visual Acuity (Early Treatment Diabetic Retinopathy Study)

Visit values and changes from baseline for BCVA score will be summarized by randomized treatment group at each visit scheduled during treatment period using continuous descriptive statistics. Only the study eye will be summarized.

8.8.2 Spectral Domain – Ocular Coherence Tomography

Visit values and changes from baseline for SD-OCT score (µm) will be summarized by randomized treatment group at each visit and time point scheduled during treatment period using continuous descriptive statistics. Only the study eye will be summarized.

DocUUID : e2994b29-81b1-4ff9-ab3b-fe25a6ed0615

Statistical Analysis Plan (SAP)

8.9 Subgroup Analysis

No pre-specified subgroup analyses will be conducted as part of this SAP.

Statistical Analysis Plan (SAP)

8.10 Interim Analysis

No planned interim analysis will be conducted as part of this SAP.

DocUUID : e2994b29-81b1-4ff9-ab3b-fe25a6ed0615

Statistical Analysis Plan (SAP)

9 CHANGES TO PLANNED ANALYSIS FROM STUDY PROTOCOL

There are no changes to planned statistical analyses indicated in the protocol.

DocUUID : e2994b29-81b1-4ff9-ab3b-fe25a6ed0615

Statistical Analysis Plan (SAP)

10 REFERENCES

1. ICH Topic E3: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95-adopted December 1995).
2. ICH Topic E9: Statistical Principles for Clinical Trials (CPMP/ICH/363/96 – adopted March 1998).

DocUUID : e2994b29-81b1-4ff9-ab3b-fe25a6ed0615

11 APPENDICES

Appendix 1 – Event of Interest (EOI)

Event of Interest (EOI)	MedDRA Terms or Search Strategy
ENDOPHTHALMITIS	Any of the following preferred term: *Endophthalmitis* *Candida endophthalmitis* *Mycotic endophthalmitis* *Eye infection* *Eye infection bacterial* *Eye infection fungal* *Eye infection chlamydial* *Eye infection staphylococcal* *Eye infection intraocular*
INCREASE IN INTRAOCULAR PRESSURE	Any of the following preferred term: *Intraocular pressure increased* *Ocular hypertension* *Angle closure glaucoma* *Borderline glaucoma* *Glaucoma* *Glaucoma traumatic* *Normal tension glaucoma* *Open angle glaucoma* *Phacolytic glaucoma* *Pseudophakic glaucoma* *Uveitic glaucoma* *Glaucomatous optic disc atrophy*
RETINAL DETACHMENT	Any of the following preferred term: *Retinal tear* *Retinal detachment*
THROMBOEMBOLIC EVENTS	Embolic and Thrombotic events SMQ (Narrow)

DocUUID : e2994b29-81b1-4ff9-ab3b-fe25a6ed0615

Statistical Analysis Plan (SAP)

Appendix 2 – Definition of INTRAOCULAR INFLAMMATION and VITREOUS HAEMORRHAGE

Event	MedDRA Terms
INTRAOCULAR INFLAMMATION	Any of the following preferred term: *Anterior chamber cell* *Anterior chamber flare* *Anterior chamber inflammation* *Aqueous fibrin* *Autoimmune uveitis* *Chorioretinitis* *Choroiditis* *Cyclitis* *Eye inflammation* *Hypopyon* *Uveitis* *Iridocyclitis* *Iritis* *Non-infectious endophthalmitis* *Ocular vasculitis* *Pseudoendophthalmitis* *Retinal vasculitis* *Retinitis* *Vitreal cells* *Vitritis*
VITREOUS HAEMORRHAGE	Any of the following preferred term: *Vitreous haemorrhage* *Vitreous haematoma*

16.1.9.2 Statistical Methods and Analysis Output

Not applicable