STATISTICAL ANALYSIS PLAN

Title:	A STUDY IN PATIENTS WITH CHORIORETINAL VASCULAR DISEASE TO EVALUATE AN AFLIBERCEPT (EYLEA®) PREFILLED SYRINGE (PFS)
Protocol:	VGFTe-OD-1881
Investigational product:	Intravitreal Aflibercept Injection
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
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Study Medical Director:	[redacted]
Date:	**01 Feb 2019**
Version:	**1**

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
AMD	Age-related macular degeneration
ATC	Anatomical Therapeutically Chemical
BCVA	Best Corrected Visual Acuity
BRVO	Branch Retinal Vein Occlusion
CRF	Case Report Form
CRVO	Central Retinal Vein Occlusion
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
ETDRS	Early Treatment Diabetic Retinopathy Study
ICH	International Conference of Harmonization
IOP	Intraocular Pressure
IVT	Intravitreal
mCNV	Myopic Choroidal Neovascularization
MedDRA	Medical Dictionary for Regulatory Activities
(MedDRA) HLT	High Level Term
(MedDRA) LLT	Low Level Term
(MedDRA) PT	Preferred Term
(MedDRA) SOC	System Organ Class
PFS	Prefilled Syringe
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SAF	Safety Analysis set
SAP	Statistical Analysis Plan
TEAE	Treatment-emergent Adverse Event
WHO	World Health Organization

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of the study. The statistical evaluation will be done according to the specifications given in the protocol and, if applicable, the corresponding amendments.

The SAP is intended to be a comprehensive and detailed description of the strategy and statistical technique to be used to confirm that the single-dose Prefilled Syringe (PFS) supports successful preparation and accurate administration of an aflibercept injection by retina specialists by using a single aflibercept treatment, and a follow-up period through day 29 data from the VGFTe-OD-1881 study.

1.1. Background/Rationale

The efficacy and safety of intravitreal (IVT) aflibercept has been well characterized across multiple indications in numerous clinical trials. Marketing authorizations have been granted for aflibercept (EYLEA®, [aflibercept] injection), in over 108 countries for the treatment of patients with neovascular "wet" age-related macular degeneration (AMD) including the United States (US), countries in the European Union (EU), Japan, and Australia. Intravitreal aflibercept injection is also approved for the treatment of patients with macular edema following central retinal vein occlusion (CRVO) in over 104 countries, macular edema following branch retinal vein occlusion (BRVO) in over 98 countries, diabetic macular edema (DME) in over 103 countries, and myopic choroidal neovascularization (mCNV) in over 95 countries. In addition to neovascular AMD, DME, and retinal vein occlusion (RVO), aflibercept is also approved in the US for the treatment of diabetic retinopathy (DR) in patients with DME.

Currently, aflibercept is available as a sterile aqueous solution for injection in single-use, glass vials. Each vial provides a usable amount to deliver a single dose of 2 mg aflibercept in a volume of 50 µL. This configuration requires withdrawal of aflibercept using a 19-gauge × 1½-inch, 5 µM, filter needle into a 1 mL syringe. Prior to injection the filter needle is replaced with 30-gauge × ½-inch injection needle. These steps are performed using aseptic technique.

To minimize the number of manipulations required to prepare the injection, Regeneron has developed a single-use 1 mL glass PFS that is externally sterilized. Each single-dose, PFS provides a usable amount to deliver a single dose of 2 mg aflibercept in a volume of 50 µL.

This study is intended to investigate if the PFS allows for successful preparation and administration by retina specialists.

1.2. Study Objectives

1.2.1. Primary Objectives

The primary objective of the study is to determine if the PFS can be used effectively and safely by retina specialists to administer the 2-mg dose of aflibercept.

1.2.2. Secondary Objectives

The secondary objective of the study is to assess ocular safety in the study eye.

1.2.3. Modifications from the Statistical Section in the Final Protocol

Not applicable

1.2.4. Modifications from the Approved Statistical Analysis Plan

Not applicable

2. INVESTIGATION PLAN

2.1. Study Design

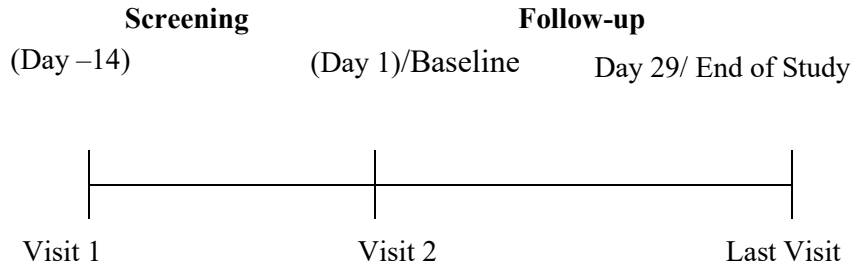
This is a phase 4, single-arm, open-label study in patients with chorioretinal vascular disease (neovascular AMD, DME, RVO, and DR in patients with DME) to evaluate handling of the aflibercept PFS. The study consists of a screening period, a single aflibercept treatment, and a follow-up period through day 29.

After providing informed consent, patients will be assessed for study eligibility at the screening visit, up to 2 weeks before the day 1/baseline visit. Screening and the day 1/baseline visit can occur on the same day. Only 1 eye will be selected as the study eye.

At the day 1/baseline visit, patients will undergo safety assessments, and will then receive a single dose of study drug, prepared (retina specialist and/or designee) and administered with the PFS by a retina specialist.

There is a follow-up period of 28 days with a window of -7 days to +14 days, during which patients will be evaluated for safety (ocular adverse events (AEs) and all [ocular and non-ocular] serious adverse events (SAEs).

Figure 1: Study Flow Diagram



Approximately 35 patients will receive a single dose of study drug based on FDA advice and not determined from power analysis.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (1998), the following analysis populations will be used for all statistical analysis:

3.1. Safety Analysis Set

The safety analysis set (SAF) includes all enrolled patients who received study drug. Treatment administration and all clinical safety variables will be analyzed using the SAF.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

Demographic and baseline assessments to be summarized will include:

- Age, gender, ethnicity, and race
- Baseline Intraocular pressure (IOP)
- Baseline Early Treatment Diabetic Retinopathy Study (ETDRS) letter score
- Baseline central retinal thickness

4.2. Medical History

Medical history will be coded according to latest available version of Medical Dictionary for Regulatory Activities (MedDRA).

4.3. Pre-Treatment / Concomitant Medication

Medications taken during the study will be recorded and will be coded to ATC codes according to the World Health Organization Drug Dictionary WHO Drug B3 v2018SEP Enhanced (this version does not include herbal dictionary).

Medications will be summarized as follows:

- **Prior medication** is defined as medication that was started before and ended before a patient received study treatment.
- **Concomitant medication** is defined as medications that are ongoing at or begin after the study treatment.
- **New medication** is defined as medications that began after the start of study treatment.

The prior, concomitant and new medication will be summarized by ATC class (ATC level 1) and subclass (ATC level 2).

Variables for concomitant medication description and analysis will include Generic name, ATC level codes, Indication, Dose/Dose Unit, Frequency, Route, start/end date and study day, Duration, Ongoing.

4.4. Exposure, Compliance, Additional Treatment to Study Treatment

Exposure

For each patient, the following variables will be used to examine exposure to study treatment for the study eye:

- The number of aflibercept injections successfully administered utilizing the PFS will be summarized.
- The extent of exposure to the investigational drug (characterized according to the number of patients exposed) will be detailed in the tables and listings.

Compliance

Not applicable, as each patient only receives a single injection.

4.5. Safety Variables

- Proportion of Patients with ≥ 10 (mmHg) Increase in Intraocular Pressure from Baseline or Pre-dose in Study Eye.
- Proportion of Patients with Pre-/Post-Injection Intraocular Pressure > 21 (mmHg), ≥ 25 (mmHg) and 35 ≥ (mmHg) in Study Eye.
- Proportion of Patients Met IOP Criteria in Any Visit through Day 29 - Study Eye.
- Change from Baseline in Best Corrected Visual Acuity (BCVA) Score by Visit.
- Change from Baseline in Central Subfield Thickness by Visit.
- Mean Change from Baseline for Pre-Injection Intraocular Pressure in Study Eye (mmHg).

4.5.1. Adverse Events and Serious Adverse Events

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug.

AEs will be collected at each visit from the time of informed consent signature until the end of the study. If the patient withdraws from the study during the screening, AEs will be collected up until the patient withdraws. If the patient withdraws at any point after receiving the first dose of study medication, AEs will be collected up until 30 days after the last dose of study drug or the termination visit, whichever is later.

AEs will be summarized as:

- **Pre-treatment AE:** Include AEs that occur after the patient has signed the informed consent, but prior to Visit 2 (Day 1, date of the patient's dose of study drug).
- **Treatment-Emergent Adverse Event (TEAE):** Treatment-emergent adverse event (TEAE) is defined as AE that is observed or reported after study drug and not later than 28 days after study drug administration. Only worsening, pre-existing AEs and new AEs reported during the treatment period (period after study drug) will be collected in the study and all TEAEs and AEs will be summarized from Day 1 to Day 29 i.e., through End of Study.

Other variables for AE description and analysis will include AE Verbatim Term, AE start date and end date/ongoing and corresponding study day, AE Duration, relationship of AE to study drug, relationship of AE to study procedure, seriousness, intensity, action due to AE, treatment of AE and outcome.

4.5.2. Ocular Safety Measures

Variables of analysis for ocular safety measures include during Day 29:

- Proportion of patients with increased intraocular pressure (IOP):

- ≥ 10 mmHg increase in IOP measurement from baseline to any pre-dose measurement
- > 21 mmHg for any pre-dose measurement
- ≥ 25 mmHg for any pre-dose measurement
- ≥ 35 mmHg at any time

Post dose IOP measurement should be the last IOP recorded.

5. STATISTICAL METHODS

All safety variables will be summarized descriptively with appropriate statistics: categorical variables by frequency (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum). Continuous variables will be described by visit and as change from Baseline, if applicable.

5.1. Demographics, Baseline Characteristics, Medical History, and Prior/ Concomitant Medication

Demographic data and baseline characteristics variables described in Section 4.1 will be summarized using descriptive statistics for SAF.

Medical/ocular history is evaluated for SAF by a frequency table, showing number of patients with medical history findings by primary system organ class (SOC), high level term (HLT) by MedDRA terms.

Prior/concomitant medication will be summarized by WHO Drug B3 v2018SEP Enhanced (this version does not include herbal dictionary) version ATC codes (ATC 3-digit class and ATC 5-digit subclass) for medication taken during the study. Separate frequency tables will be displayed for patients with prior medications, new medications and concomitant medications by the time periods as described in Section 4.3. Concomitant medications will be summarized by Day 1 up to Day 29 (End of study).

5.2. Subject Disposition

The following categories for patient disposition will be summarized descriptively:

- The total number and percentage of patients received study medication
- The number and percentage of patients in safety analysis set
- The total number and percentage of patients who discontinued the study with the reasons for discontinuation

The following listings will be provided to assess the patient disposition:

- A listing of patients treated but not enrolled and patients enrolled but not treated if any
- A listing of patients who were withdrawn from the study, along with reasons for discontinuation
- Listing of major protocol deviations: violation of inclusion/exclusion criteria; post-enrollment deviations which will impact assessment of endpoints

5.3. Extent of Study Treatment Exposure and Compliance

The variables for dose exposure described in Section 4.4 will be summarized by frequency for study eye in SAF population.

5.4. Analysis of Safety Data

The safety variables as described in Section 4.5 will be analyzed on SAF population through Day 29 after final study database lock.

5.4.1. Adverse Events

AE summaries will be constructed displaying frequencies and proportions of patients reporting AEs within each SOC in decreasing order of total frequency according to the numbers of patients reporting the SOC and the AE within the SOC (not number of reports).

AEs will be classified as Pre-treatment AEs and TEAEs, and will further be summarized by the following categories:

- Ocular AEs in the study eye
- Ocular AEs in the fellow eye
- Non-ocular SAEs

SAEs, drug-related AEs, drug-related SAEs, and TEAEs leading to discontinuation will be summarized in the same way as described for TEAE.

TEAEs leading to permanent treatment discontinuation will be listed and summarized.

TEAEs in the study eye related to the injection procedure and those related to the study medication will be summarized separately.

An overall summary of the AE profile for aflibercept in this study will be provided.

Summaries of all TEAEs will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity, presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT

Deaths and other SAEs will also be listed and summarized.

A listing will be constructed that includes the patient identification, category of AE (ocular study eye or fellow eye, non-ocular), AE, MedDRA term, seriousness, severity, causality, elapsed time to onset, duration, and outcome.

Intraocular inflammation will be tabulated and listed. The detailed definition of the preferred terms for intraocular inflammation is presented in Appendix 10.2.

5.4.2. Ocular Safety Measures

Baseline IOP and change from Baseline in IOP to each scheduled assessment visit will be summarized with descriptive statistics for study eye and fellow eye. Assessment of significant values or increases will be made and summarized for the proportion of patients with increased IOP in the study eye or fellow eye with the categories defined in Section 4.5.2.

5.4.3. Best Corrected Visual Acuity

Baseline BCVA and change from Baseline in BCVA to each scheduled assessment visit will be summarized with descriptive statistics for study eye and fellow eye. The listing of summary scores for standard Early Treatment Diabetic Retinopathy Study (ETDRS) for study eye will also be provided.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline

Unless otherwise specified, the Baseline assessment for all measurements will be the last available valid measurement taken prior to the administration of investigational product.

6.2. Unscheduled Assessments

Assessments taken outside of protocol allowable windows will be displayed according to the case report form (CRF) assessment recorded by the investigator.

Unscheduled assessments will not be included in the summaries.

Early termination visit (ET): If a subject prematurely discontinues they are asked to come for an early termination visit. Visit based information of this visit will only be used in the tabulation if the visit was performed 4 weeks, i.e., 28 days (-7 to +14 days) after baseline visit consisting of the end-of-study assessments described in Section 10.1. ET visits outside this window will not be used for analyses and handled in the same way as unscheduled assessments (see above).

6.3. Handling of Patients Who Discontinue

Patients who discontinue this study will not be replaced.

6.4. Handling of Missing Data

6.4.1. General Rules

When appropriate, the following rules will be implemented so as not to exclude patients from statistical analyses due to missing or incomplete data:

- AE variables

  For some AEs it is important to determine whether the AE started before or after the first active aflibercept injection. If the AE start date is partially missing, it will be imputed by the latest possible date (considering other available data, e.g., stop date) to be conservative.

- Prior/concomitant medication

  For the tabulation of prior and concomitant medication, partially missing start dates of the medication will be imputed by the earliest possible time point, partially missing stop dates will be imputed by the latest possible time point.

7. INTERIM ANALYSIS

No formal interim analysis is planned.

8. SOFTWARE

All analyses will be done using SAS Version 9.4 or higher.

9. REFERENCES

ICH. (1998, February 5). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

10. APPENDIX

10.1. Schedule of Time and Events:

Table 1: Schedule of Time and Events

Study Procedure	Screening[1] Visit 1	Combined Screening/Baseline Visit[1] Visit 1/2	Baseline[1] Visit 2	End of Study Visit 3
Day	-14 to -1	1	1	29 (-7 to +14 days)
Screening/Baseline:				
Inclusion/exclusion	X	X[2]		
Informed consent	X	X[2]		
Medical history	X	X[2]		
Demographics	X	X[2]		
Treatment:				
Review of concomitant meds	X	X[2]	X[2]	X
Administer intravitreal aflibercept		X[3]	X[3]	
Safety:				
Slit lamp examination	X	X[2]	X[2]	X
Indirect ophthalmoscopy	X	X[4]	X[4]	X
SD-OCT	X	X[2]	X[2]	X
ETDRS 4M BCVA	X	X[2]	X[2]	X
Intraocular Pressure	X	X[5]	X[5]	X
Adverse events (ocular study eye and all serious adverse events)	X	X	X	X

SD-OCT=spectral domain optical coherence tomography, ETDRS= Early Treatment Diabetic Retinopathy Scale, BCVA= Best Corrected Visual Acuity

10.2. Intraocular Inflammation:

The preferred terms for the definition of intraocular inflammation below are based on MedDRA version 21.1.

Intraocular Inflammation

Preferred term
Anterior chamber cell
Anterior chamber fibrin
Anterior chamber flare
Anterior chamber inflammation
Aqueous fibrin
Autoimmune uveitis
Chorioretinitis
Choroiditis
Cyclitis
Endophthalmitis
Eye infection intraocular
Eye inflammation
Hypopyon
Infective iritis
Infective uveitis

Infectious iridocyclitis
Iridocyclitis
Iritis
Non-infectious endophthalmitis
Non-infective chorioretinitis
Pseudoendophthalmitis
Serpiginous choroiditis
Uveitis
Vitreal cells
Vitreous fibrin
Vitritis

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