REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
VERSION: FINAL V1.0

Clinical Study Protocol Title:	A Study in Patients with Diabetic Macular Edema or Neovascular Age-Related Macular Degeneration to Evaluate a High Dose Aflibercept (8 mg) Prefilled Syringe
Compound:	Aflibercept 8 mg
Protocol Number:	VGFTe-HD-OD-22105
Clinical Phase:	Phase 3b
Sponsor:	Regeneron Pharmaceuticals, Inc.
Versions/Dates:	Original Statistical Analysis Plan / February 1, 2024

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
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
BP	Blood pressure
CRF	Case report form
CST	Center Subfield Thickness
DME	Diabetic macular edema
EDC	Electronic data capture
ET	Early termination
ETDRS	Early Treatment Diabetic Retinopathy Scale
FDA	Food and Drug Administration
HR	Heart rate
ICF	Informed consent form
IOP	Intraocular pressure
MedDRA	Medical Dictionary for Regulatory Activities
nAMD	Neovascular age-related macular degeneration
PFS	Pre-filled syringe
PT	Preferred term
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD-OCT	Spectral domain optical coherence tomography
SOC	System organ class
TEAE	Treatment-emergent adverse event
WOCBP	Women of childbearing potential

1. OVERVIEW

The SAP is intended to be a comprehensive and detailed description of the statistical methods, timing of analyses and analysis presentation to be used for the study specified in protocol VGFTe-HD-OD-22105, originally dated 14-JUN-2023.

1.1. Study Description and Objectives

This is a phase 3b, single-arm, open-label study in patients with Neovascular "wet" Age-related Macular Degeneration (nAMD) or Diabetic Macular Edema (DME) to evaluate the use of the aflibercept 8 mg pre-filled syringe (PFS).

1.1.1. Primary Objective(s)

The primary objective of the study is to determine if the PFS can be used successfully by retina specialists to administer the 8 mg dose of aflibercept.

1.1.2. Secondary Objective(s)

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

1.2. Statistical Hypothesis

There is no formal statistical hypothesis in this study.

1.3. Interim Analysis

No interim analysis is planned.

1.4. Modifications from the Statistical Section in the Final Protocol

There are no modifications from the statistical section in the final protocol.

1.5. Revision History for SAP Amendments

This is the original version of the SAP.

2. INVESTIGATION PLAN

2.1. Study Design

This is a phase 3b, single-arm, open-label study in patients with nAMD or DME to evaluate the use of the aflibercept 8 mg PFS. The study consists of a screening period, a single aflibercept injection on day 1, and a follow-up period through Day 29.

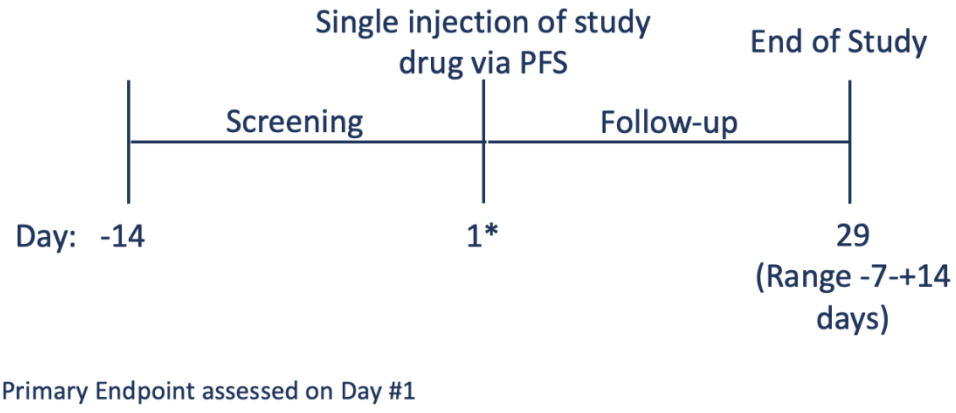
After providing informed consent, patients are assessed for study eligibility at the screening visit, to be scheduled up to 2 weeks before the day 1 (baseline) visit. Screening and the day 1 (baseline) visit may also occur on the same day. Only 1 eye is selected as the study eye by the investigator.

At the day 1 (baseline) visit, patients undergo safety assessments followed by a single injection of the study drug, prepared by a retina specialist and/or technician, 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 are monitored and evaluated for safety. Ocular adverse events (AE) in the study eye and all ocular and non-ocular serious adverse events (SAE) are captured.

The study flow diagram is shown in Figure 1.

Figure 1: Study Flow Diagram



PFS = prefilled syringe

2.2. Sample Size and Power Considerations

The sample size of approximately 35 patients for this study is based on US Food and Drug Administration (FDA) advice and is not determined from power analysis.

3. ANALYSIS SETS

The following defines the set(s) of subjects whose data is used for statistical analysis.

3.1. Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) includes all enrolled patients who received any study drug. Treatment administration and all clinical safety variables is analyzed using the SAF.

4. GENERAL STATISTICAL ANALYSIS CONSIDERATIONS

For continuous variables, descriptive statistics include the following information: the number of patients reflected in the calculation (n), mean, median, standard deviation, 1st quartile, 3rd quartile, minimum, and maximum. Continuous variables are described by visit and as change from Baseline, if applicable.

For categorical or ordinal data, frequencies and percentages are displayed for each category.

All levels of the categorical variable are included. If there are observations where the level of the categorical variable is missing, a separate category titled "Not Reported" will be created. For categorical variables that are ordinal in nature, the order in which the levels of the categories are displayed will be consistent with the natural ordering of the category levels.

Percentages are calculated for each level of the categorical variables with respect to the total number of patients.

5. PATIENT DISPOSITION

The following categories for patient disposition are summarized descriptively:

- The total number of screened patients who have signed the informed consent form (ICF), the number of screen failure and the reasons for screen failure.
- The total number of enrolled patients
- The total number and percentage of patients who prematurely discontinued the study with the reasons for discontinuation
- The total number and percentage of patients who had protocol deviations with the type of deviation

6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

6.1. Demographics

The following demographic variables are summarized using descriptive statistics on the SAF:

- Age at screening (year)
- Age categories (<40 years, 40 – <65 years, >=65 years)
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White, Other, and Not Reported)
- Ethnicity (Hispanic/Latino, Not Hispanic or Latino)
- Disease (nAMD, DME)
- Prior anti-VEGF treatment in the study eye (yes/no)
- Duration of prior anti-VEGF treatment in the study eye (days)
- Prior 2mg aflibercept treatment in the study eye (yes/no)
- Duration of prior 2mg aflibercept treatment in the study eye (days)
- Prior 8mg aflibercept treatment in the study eye (yes/no)
- Duration of prior 8mg aflibercept treatment in the study eye (days)

6.2. Baseline Disease Characteristics

The following disease characteristics in the study eye are summarized using descriptive statistics on the SAF:

- Baseline Best Corrected Visual Acuity (BCVA) (letters) Score assessed using the 4-meter Early Treatment Diabetic Retinopathy Study (ETDRS) scale
- Baseline Center Subfield Thickness (CST) (microns) assessed by Spectral domain optical coherence tomography (SD-OCT)
- Baseline intraocular pressure (IOP) (mmHg)

6.3. Medical History

Patient medical history is coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The frequency and percentage of ocular and non-ocular medical/surgical history is summarized separately by primary system organ class (SOC), and preferred term (PT) using the SAF.

7. EFFICACY DATA

No efficacy data is analyzed in this study.

8. HYPOTHESIS TESTING METHODS AND MULTIPLICITY CONTROL

There are no statistical hypotheses in this study.

9. SUMMARY OF EXPOSURE DATA

9.1. Investigation Study Drug Exposure and Compliance

The primary endpoint is the proportion of investigator-determined successful 8 mg aflibercept PFS injections in the SAF. Successful injection in a given patient is defined as administration of the prescribed dose consistent with the instructions for use as assessed by the injecting physician.

The investigator's determination of a successful 8 mg aflibercept PFS injection is recorded as a "yes" or "no" in the source documents and electronic data capture (EDC) system and summarized descriptively (proportion "yes" and "no" responses).

Exposure

The number and proportion of patients in the SAF who successfully received aflibercept injection in the study eye utilizing the PFS are presented.

Compliance

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

9.2. Duration of Follow-up

Not applicable, duration of follow-up is not be summarized.

9.3. Prior and Concomitant Medications

Medications taken during the study is coded using the World Health Organization Drug Dictionary.

Medications are summarized as follows on the SAF:

- Prior medication is defined as medication that starts before and ends before the first study treatment.
- Concomitant medication is defined as medication that is ongoing at the time of the first study treatment or begins after the first study treatment.
- New medication is defined as medication that begins after the start of study treatment.

The prior, concomitant and new medications are summarized by Anatomical Therapeutic Chemical (ATC) class (ATC level 2) and subclass (ATC level 4).

9.4. Prior and Concurrent Procedures

Procedures performed during the study will be coded using MedDRA.

Treatment-emergent procedures, defined as having been performed on or after the start of study treatment, will be summarized in the SAF by MedDRA preferred term.

10. ANALYSIS OF SAFETY DATA

Safety data are analyzed on the SAF.

10.1. Adverse Events

All new or worsening AEs occurring between signing of the ICF and the end of the study are recorded and coded using MedDRA.

AEs are summarized with incidence tables. AE incidence tables present the number (n) and percentage (%) of patients experiencing an AE sorted by decreasing frequency of SOC and PT. Multiple occurrences of the same event in a patient are only be counted once in the summary. For tables showing AE severity, for instances where a patient has multiple occurrences of the same PT or SOC, only the worst severity is counted in the summary.

The AE summaries are presented for treatment-emergent AEs (TEAE). TEAEs are AEs with either: initial onset, increase in severity, or exacerbation to serious after the first dose of study treatment.

The following summaries for TEAEs are presented:

- Overview of TEAEs
- Ocular TEAEs of the study eye by primary SOC and PT
- Ocular TEAEs of the fellow eye by primary SOC and PT
- Ocular TEAEs of the study eye related to study drug by primary SOC and PT
- Ocular TEAEs of the study eye related to study conduct by primary SOC and PT
- Serious ocular TEAEs of the study eye by primary SOC and PT
- Serious non-ocular TEAEs by primary SOC and PT
- Serious ocular TEAEs of the study eye related to study drug by primary SOC and PT
- Serious ocular TEAEs of the study eye related to study conduct by primary SOC and PT
- Ocular TEAEs of the study eye by primary SOC, PT, and severity
- Non-ocular TEAEs of the study eye by primary SOC, PT, and severity
- Treatment-emergent intraocular inflammation of the study eye by primary SOC and PT. The detailed definition of the preferred terms for intraocular inflammation is presented in Appendix 13.2.

10.2. Vital Signs

The following vital signs parameters are recorded and summarized according to the Schedule Events in Appendix 13.1 :

- Body temperature
- Sitting blood pressure (systolic and diastolic)

- Pulse rate

Vital sign values and change from baseline in vital signs values to Day 29 visit are summarized with descriptive statistics.

10.3. Other Safety Data

10.3.1. Intraocular Pressure

Pre-dose IOP (mmHg) in the study eye is summarized by visit using descriptive statistics and graphical presentations. Change from baseline in pre-dose IOP at Day 29 visit is summarized using descriptive statistics.

The following additional safety variables are also analyzed:Proportion of patients with ≥ 10 mmHg increase in IOP from baseline (pre-dose) in the study eye.

- Proportion of patients with pre-injection or post-injection IOP > 21 mmHg, ≥ 25 mmHg and ≥35 mmHg in the study eye.
- Proportion of patients who met certain IOP criteria at any visit in the study eye. These IOP criteria are as follows:
  - Proportion of patients with ≥ 10 mmHg increase in IOP measurement from Baseline to any pre-dose measurement
  - Proportion of patients with > 21 mmHg for any pre-dose measurement
  - Proportion of patients with ≥ 25 mmHg for any pre-dose measurement
  - Proportion of patients with ≥ 35 mmHg at any time

10.3.2. Other Ocular Study Procedures

BCVA and change from baseline in BCVA in the study eye are summarized by visit with descriptive statistics.

CST and change from baseline in CST in the study eye are summarized by visit with descriptive statistics.

11. DATA CONVENTIONS

11.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline assessment for all measurements is the last available measurement prior to the administration of investigational product.

11.2. Data Convention

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified.

11.3. Data for Non-Efficacy Endpoints

Medication missing/partial dates

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

If the medication start date or stop date is partially missing, the partial date is displayed in the listings.

Adverse events

If the intensity of a TEAE is missing, it is classified as “severe” in the frequency tables by intensity of TEAEs. If the assessment of relationship of a TEAE to the investigational product is missing, it is classified as related to the investigational product.

AEs with partial start dates are imputed based on the following rules:

- If AE partial start date indicates it is before the first dose of study drug, then it is imputed as the latest possible date
- If AE partial start date has the same partial date as the dose of study drug, then it is imputed as the date of the dose of study drug
- If AE partial start date indicates it is after the dose of study drug, then it is imputed as the earliest possible date.
- If imputed AE start date is later than AE end date, then the AE start date is imputed to the AE end date.

Deaths

For the listings, missing date of death is imputed with the corresponding adverse event end date.

11.4. Assignment of Data to Visit Windows and Unscheduled Assessments

Unscheduled Assessments

Assessments taken outside of protocol allowable windows are displayed according to the case report form (CRF) assessment recorded by the investigator. Unscheduled assessments are not included in the summaries.

Visit Windows

The visits used for the analysis are based on the nominal visits, i.e., according to the CRF assessment recorded by the investigator. No visit windows are further defined.

If more than one value is available for a given visit, the visit value actually used for statistical summaries and analyses is as follows:

- The last non-missing repeated measurement, if respective visit is before start of treatment.
- The first non-missing repeated measurement, if respective visit is after start of treatment.

Early termination visit (ET)

If subjects prematurely discontinue, they are asked to come for an early termination visit. Visit based information of this visit are only 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 Appendix 13.1. ET visits outside this window are not used for analyses and handled in the same way as unscheduled assessments.

12. 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.

13. APPENDIX

13.1. Schedule of Time and Events

Table 1: Schedule of Time and Events

	Screening Visit[1]	Combined Screening/Baseline Visit[1]	Baseline Visit[1]	End of Study Visit
Study Procedure	**Visit 1**	**Visit 1 and 2**	**Visit 2**	**Visit 3**
Day	–14 to 1	1	1	29 (–7 to +14)
Screening/Baseline:				
Inclusion/Exclusion	X	X[2]		
Informed Consent (ICF)	X	X[2]		
Medical History	X	X[2]		
Demographics	X	X[2]		
Pregnancy Test Urine (WOCBP)[7]	X	X[2]		
Treatment:				
Review of Concomitant Meds	X	X[2]	X[2]	X
Administer Intravitreal Aflibercept via PFS		X[3]	X[3]	
Safety:				
BCVA (ETDRS) and refraction	X	X[2]	X[2]	X
IOP	X	X[4]	X[4]	X
Slit lamp examination	X	X[2]	X[2]	X
Indirect ophthalmoscopy[5]	X	X	X	X
SD-OCT[6]	X	X[2]	X[2]	X
Vital signs (Temperature, BP, HR)	X	X[2]	X[2]	X
Adverse events (ocular study eye and all serious adverse events)	X	X	X	X

BCVA = Best Corrected Visual Acuity, BP = Blood pressure, ETDRS = Early Treatment Diabetic Retinopathy Scale, HR = Heart rate, ICF = Informed consent form, IOP = Intraocular pressure, PFS = Pre-filled syringe, SD-OCT = Spectral domain optical coherence tomography, WOCBP = women of childbearing potential.

1. The screening and baseline visits may be conducted separately (visit 1 and visit 2) or may be combined (visit 1 and 2); however, assessments and procedures do not need to be duplicated.
2. Must be completed before administration of aflibercept 8 mg
3. A single intravitreal injection of aflibercept 8 mg will be administered on day 1 or as part of the combined screening/baseline visit. The pharmacy manual will contain instructions for use. Patients will be observed for approximately 30 minutes following study drug injection.
4. IOP (bilateral) will be measured at all study visits. On days when the study drug is administered, IOP should be measured pre-dose (bilaterally) and approximately 30 minutes after administration of the study drug (study eye only). IOP will be measured using Goldmann applanation tonometry or Tono-pen™, and the same method of measurement must be used in each patient throughout the study.
5. Indirect ophthalmoscopy should be performed pre-dose and immediately after administration of the study drug (study eye only) and at the end of study visit by the investigator.
6. The same SD-OCT imaging system used at the screening and baseline visit(s) must be used at all follow-up visits in each patient. Images will be taken in both the eyes before dosing and after administration of the study drug in the study eye only.
7. For women of childbearing potential (WOCBP), a negative urine pregnancy test at screening is required for eligibility.

13.2. Intraocular Inflammation:

Prior to database lock these preferred terms will be updated as necessary based on the current MedDRA version.

Intraocular Inflammation

Preferred term
Anterior chamber cell
Anterior chamber fibrin
Anterior chamber flare
Anterior chamber inflammation
Aqueous fibrin
Autoimmune uveitis
Candida endophthalmitis
Chorioretinitis
Choroiditis
Cyclitis
Endophthalmitis
Eye infection intraocular
Eye inflammation
Hypopyon
Infective iritis
Infective uveitis
Infectious iridocyclitis
Iridocyclitis
Iritis
Mycotic endophthalmitis
Non-infectious endophthalmitis
Non-infective chorioretinitis
Pseudoendophthalmitis
Uveitis
Vitreal cells
Vitreous fibrin
Vitritis

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