US Specific Statistical Analysis Plan

Protocol Title:	A Randomized, Double-masked, Phase 3 Study of ABP 938 Efficacy and Safety Compared to Aflibercept (Eylea®) in Subjects with Neovascular Age-related Macular Degeneration
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original – US (v1.0)	09SEP2019	NA
v2.0	26May2022	Major updates: 1. add primary estimand of the study to meet regulation obligation per protocol amendment 3. (section 9.5.1) 2. update the analysis method in section 9.5.2.1-9.5.2.3 to use stratified Newcombe confidence limits (with Mantel-Haenszel weights) due to potential non-convergence in the original statistical model. 3. update ADA windows to align with DMC agreed approach (section 5.1) and add Treatment boosted ADA definition (section 9.6.8). 4. add COVID-19 related information in disposition, exposure, AEs and IPD sections (section 5.3, 9.2, 9.3, 9.6.2, 9.6.9) based on release of Amgen standard COVID-19 shells. 5. Add detailed search strategies for event of interest (EOI) in Appendix 1 and analyses of Intraocular inflammation and vitreous hemorrhage and an Appendix 2 (section 9.6.1). 6. add “Subjects with Fellow Eye treated prior to week 8 (Y/N)” into sensitivity analysis and A subgroup analysis: The "Analysis of Change from Baseline in Best Corrected Visual Acuity at Week 8 by Subgroup" based on the protocol amendment 2 fellow eye related updates. 7. update covariate section to exclude CNV and CST from subgroup analysis. (section 4.1) since CNV and CST do not have a clear cutoff to define disease severity and subgroup analysis cannot be performed. Minor editorial changes: 1. Update List of Abbreviations, text in secondary efficacy endpoint, study design section, study period, ADA section and add fellow eye in

		the through week 8 period definition per Protocol Amendment 2. 2. Update NRI wording and total IP exposure duration and add text to show that how imaging assessments (CNV area size and CST values) are processed in database (section 5.1). Clarify definition of “TEAE post week 16”, and “AEs leading to discontinuation from IP/study” in alignment with the final AE CRF and TEAE for Fellow eye (section 5.3) and change Duration of disease algorithm to be in Weeks. (section 9.4).

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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AMD	age-related macular degeneration
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BCVA	best corrected visual acuity
CDISC	standard Clinical Data Interchange Standards Consortium
CI	confidence interval
CNV	choroidal neovascularization
COVID-19	Coronavirus Disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CST	central subfield thickness
CTCAE	Common terminology Criteria for Adverse Events
DMC	data monitoring committee
ECG	electrocardiogram
EDC	electronic data capture
EOI	event of interest
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiography
FAS	Full Analysis Set
FDA	Food and Drug Administration
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IOP	intraocular pressure
IP	investigational product
IRB	institutional review board
IV	intravenous
IVT	intravitreal
IXRS	Interactive Web/Voice Response System
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities

NCI	National Cancer Institute
OCT	optical coherence tomography
PK	pharmacokinetic(s)
PP	per protocol
PT	preferred term
SAP	statistical analysis plan
SDTM	Standard Data Tabulation Model
SD-OCT	spectral domain optical coherence tomography
TEAE	treatment-emergent adverse event
WBC	white blood cell

1. Introduction

The purpose of this US-specific Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for ABP 938 study 20170542 (version 4.0, dated 16May2022) and the additional analyses to support the BLA submission in the US. The scope of this plan includes the primary analysis and the final analysis that are planned and will be executed by the designated contract research organization (CRO), Parexel International.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	***Primary efficacy endpoint***
To assess the efficacy of ABP 938 compared to aflibercept.	Change from baseline in best corrected visual acuity (BCVA) as measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score at week 8
	Secondary efficacy endpoints
	Proportion of subjects who maintained vision at week 52, where a subject was classified as maintaining vision if he/she lost fewer than 15 letters in ETDRS letter score compared to baseline
	Change from baseline in BCVA as measured by ETDRS letter score over the study duration
	Proportion of subjects who gained at least 10 letters of vision at week 8 and proportion of subjects who gained at least 15 letters of vision at week 52 as compared to baseline
	Change from baseline in choroidal neovascularization (CNV) area size as measured by fluorescein angiography (FA) and central subfield thickness (CST) as measured by spectral domain optical coherence tomography (SD-OCT) over the study duration
Secondary	
To assess the safety and immunogenicity of ABP 938 compared to aflibercept.	Treatment-emergent adverse events, adverse events of interest (EOIs), and serious adverse events
	Incidence of antidrug antibodies (ADAs)

Primary estimand:

The primary estimand is the difference in change from baseline in BCVA at week 8 between the ABP 938 group and the aflibercept group in subjects with neovascular (wet) age-related macular degeneration (AMD) who are randomized, regardless of missing or

discontinuing investigational product administration to the study eye, or use of additional medications for AMD in the study eye prior to observing BCVA at week 8.

2.2 Hypotheses and/or Estimations

The study will assess the hypothesis that there are no clinically meaningful differences between ABP 938 and aflibercept treatment arms in the primary efficacy endpoint: BCVA change from baseline at week 8. For the marketing application globally, this primary efficacy endpoint will be evaluated by comparing the 2-sided 95% Confidence Interval (CI) of the mean difference between ABP 938 and aflibercept arms with an equivalence margin of (-3.9, 3.9). For the BLA submission in the US, the primary endpoint will be evaluated by comparing the 2-sided 90% CI (rounded to the nearest integer) with an equivalence margin of (-3, 3).

3. Study Overview

3.1 Study Design

This is a randomized, double-masked, active controlled multiregional clinical study in adult subjects with neovascular Age-related Macular Degeneration (wet AMD). Approximately 566 subjects (including at least 30 subjects from East Asia) will be randomized in a masked 1:1 ratio to receive 2 mg (0.05 mL) of either ABP 938 (Treatment Group A) or aflibercept (Treatment Group B) administered by intravitreal (IVT) injection every 4 weeks for the first 3 doses (i.e., baseline/day 1, week 4, and week 8). Randomization will be stratified by geographic region and disease severity (baseline BCVA < 64 letters vs. ≥ 64 letters).

At week 8, subjects will be assessed for the primary endpoint (BCVA change from baseline as measured by ETDRS). Subjects will then be re-randomized at week 16 in a masked fashion such that:

- Subjects initially randomized to ABP 938 (Treatment Group A) will continue to receive ABP 938 by IVT injection every 8 weeks from week 16 until week 48
- Subjects initially randomized to aflibercept (Treatment Group B) will be re-randomized in a 1:1 ratio to either continue on aflibercept (Treatment Group B1) or transition to ABP 938 (Treatment Group B2) by IVT injection every 8 weeks from week 16 until week 48

Re-randomization will be stratified using the same factors as the initial randomization.

Subjects who are unable to complete the week 16 visit within the visit window will not be re-randomized, will be discontinued from the study, and will be asked to return to

complete an end-of-study (EOS) visit within 28 days from determining that the subject will discontinue from the study. An end-of-study visit will be conducted at week 52 for subjects that complete the study. The study design and treatment schema are presented in Figure 1.

The primary analysis for the study is planned when all subjects reach week 24 or terminate early. This analysis will comprise at least 24 weeks of efficacy, safety, and immunogenicity data. The final analysis is planned when all enrolled subjects complete the week 52 visit or terminates early. An external, independent data monitoring committee (DMC) will evaluate the safety data throughout the study.

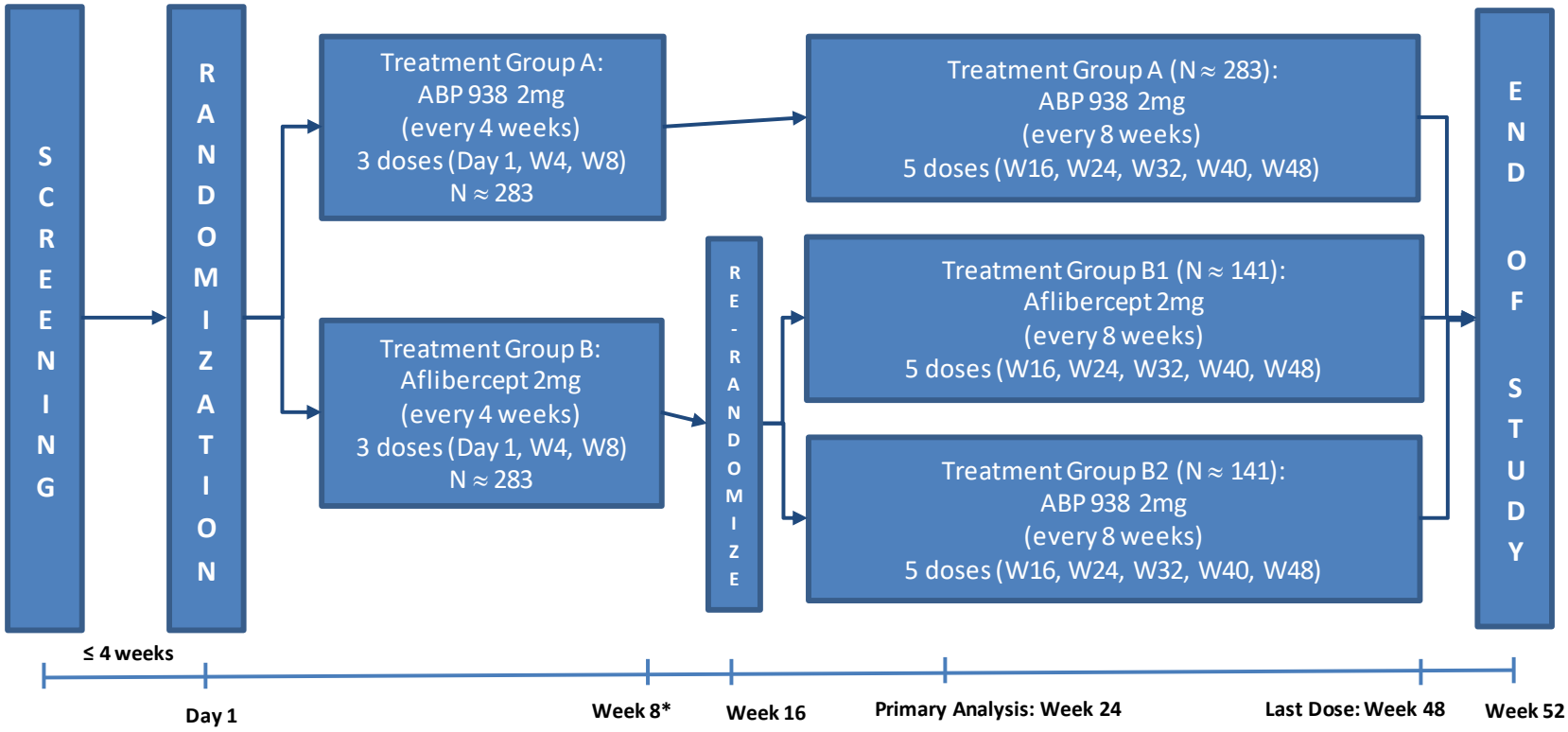
The treatment of the fellow eye is allowed starting at baseline (day 1) if needed.

Approximately 32 subjects will be consented and enrolled into a Pharmacokinetic (PK) substudy. These subjects will have a PK sample collected predose (within 60 minutes before day 1 dose) and postdose at day 1 (approximately 24 hours after day 1 dose), with an allowable window -6 hours to +24 hours (ie, 18 hours to 48 hours after day 1 dose) and postdose at week 8 (approximately 24 hours after week 8 dose), with an allowable time window of -6 hours to +24 hours (ie, 18 hours to 48 hours postdose).

If it is anticipated that the fellow eye will need to be treated prior to the week 8 postdose PK sample, then the subject should not be enrolled into the PK substudy. If an enrolled PK substudy subject develops a requirement for fellow eye treatment prior to week 8 postdose PK sample, no further PK samples will be collected.

If the need for treating the fellow eye is identified at the week 8 visit, then the fellow eye must be treated after the week 8 postdose PK sample has been drawn for those subjects included in the PK substudy.

Figure 1 Study Schematic



*Primary Endpoint assessment will be performed at Week 8.

3.2 Sample Size

Approximately 566 subjects (including at least 30 East Asian subjects) will be randomized in a 1:1 ratio initially to receive ABP 938 (Treatment Group A) or aflibercept (Treatment Group B). The total sample size will provide > 90% power to demonstrate equivalence at a 2-sided significance level of 0.025 with an equivalence margin of (-3.9, 3.9) (global) on the primary efficacy endpoint BCVA change from baseline at week 8, assuming a true mean difference of 0 in the primary endpoint between the 2 groups, a standard deviation of 12.5 letters, and a 2% dropout by week 8. It will also provide approximately 90% power (with rounding of CI) to demonstrate equivalence at a 2-sided significance level of 0.05 with a margin of (-3, 3) (US). In addition, the number of East Asian subjects (i.e., at least 30) was chosen to enable an assessment of the treatment difference within East Asian subjects with reasonable accuracy and precision, while ensuring the study recruitment is feasible and can be completed in a timely manner.

4. Covariates and Subgroups

4.1 Planned Covariates

Unless stated otherwise, the following stratification factors will be adjusted as covariates in models or will be used to examine treatment effect in subgroups:

- Geographic region (East Asia, Europe, North America)
- Disease severity (baseline BCVA < 64 letters vs. ≥ 64 letters).

In addition, the following covariates may be used for further exploration in subgroups or as covariates:

- Age (< 65 years vs. ≥ 65 years)
- Race (White vs. Non-White)
- Gender
- CNV area size (excluding from subgroups)
- CST (excluding from subgroups)
- Subjects with Fellow Eye treated prior to week 8 (Y/N)
- Baseline BCVA measurement (continuous)

Covariate values may be discordant if collected via CRF and IXRS. Analyses that are intended to evaluate the treatment effect and include stratification variables as covariates in the model will be based on the CRF stratification values, regardless of the

subject's IXRS stratification values, to provide unbiased estimates of the effects of treatment and stratification variables without loss of efficiency (Ke *et al*, 2017).

4.2 Subgroups

Please refer to Section 4.1.

For subgroup analyses where the subgroup factor is a stratification variable, an analysis similar to the primary analysis (except the inclusion of the subgroup factor) should be done for each subgroup defined by the CRF values of the subgroup factor.

5. Definitions

5.1 General

Actual Treatment Received

The actual treatment received on an eye level (separately for the study eye and the fellow eye) is the IP treatment the eye actually received, regardless of what the subject was randomized to. For each of the "through week 8", "through week 16", and "post week 16" study periods (see definition of Study Period later in this section), if an eye received both ABP 938 and aflibercept, the actual treatment received will be based on the majority of the IP treatment the eye received during that study period. In the case of a tie, the actual treatment received will be assigned to ABP 938. For the "entire study" study period, the actual treatment sequence for subjects who were re-randomized and treated post re-randomization will be defined based on the actual treatments received during the "through week 16" and "post week 16" study periods.

The actual treatment received on a subject level will be set to be same as the actual treatment received for the study eye.

Baseline

Unless stated otherwise, the baseline at the subject level (aka study baseline) is defined as the last non-missing assessment taken prior to the first dose of IP the subject received (see definition of first dose date for the subject later in this section). In cases where baseline assessments are taken on the same day as the first dose of IP, and either no times are reported or the IP and assessment times are the same, it will be assumed that these assessments are taken prior to IP being administered. For subjects who are randomized but not dosed after the randomization, the baseline is defined as the last non-missing assessment prior to or on the date of randomization.

The baselines at the eye level for study eyes and fellow eyes are defined according to the first dose date of the respective eye (see definitions of the first dose date for the study eye and the fellow eye later in this section).

Change from Baseline

Change from baseline at the subject level or eye level is defined as (value at post-baseline visit – value at baseline), where subject or eye level post-baseline and baseline values are used, respectively. Refer to definitions of baseline for the subjects, study eyes, and fellow eyes above.

Concomitant and Prior Medication

Prior medications are defined as medications with a stop date prior to first dose of IP the subject received (see definition of first dose date for the subject). Concomitant medications are defined as any medications ongoing at the start of IP treatment for the subject or with a start date on or after the first dose date.

End of Study (EOS) Date

The EOS date is the date recorded on the End of Study page of the CRF.

First Dose Date

- First Dose Date for the Study Eye

It is defined as the date on which the study eye is administered the first dose of IP.

- First Dose Date for the Fellow Eye

It is defined as the date on which the fellow eye is administered the first dose of IP.

- First Dose Date for the Subject

It is defined as the date the subject received the first dose of IP (i.e., earlier of the first dose dates of study eye and fellow eye). According to the protocol, it is expected to be the same as the first dose date for the study eye.

Last Dose Date

- Last Dose Date for the Study Eye

It is defined as the date on which the study eye is administered the last dose of IP.

- Last Dose Date for the Fellow Eye

It is defined as the date on which the fellow eye is administered the last dose of IP.

- Last Dose Date for the Subject

It is defined as the later of last dose date for the study eye and the fellow eye.

Last observation carried forward (LOCF)

A method of imputation where missing post-baseline data will be imputed by carrying forward the last non-missing post-baseline value for that endpoint. Baseline values will not be carried forward.

Non Responder Imputation (NRI)

A method of imputation where subject with missing post-baseline value of a binary endpoint will be imputed as a non-responder, regardless of the reasons for missing data.

Disease Duration

The disease duration is the number of weeks from the date of diagnosis of wet AMD to the date of randomization, which will be derived based on the table below. No imputation will be done for disease diagnosis date, but to avoid disease duration of zero, 1 month (or 4.34524 weeks) may be added.

Table 1: Calculation of the Duration of wet AMD

Observed portion	Missing portion	Formula to Calculate Duration
Year, Month, Day		(Date of Randomization – Date of wet AMD Diagnosis + 1)/365.25
Year, Month	Day	[Year(Date of Randomization)-Year(Date of wet AMD Diagnosis)]+ [Month(Date of Randomization)-Month(Date of wet AMD Diagnosis)]/12*
Year	Month, Day	[Year(Date of Randomization)-Year(Date of wet AMD Diagnosis)] *

*if the duration equals 0, add 1 month or 4.34524 weeks.

Study Day 1

Study day 1 is defined as the first day of IP the subject received (see definition of first dose date for the subject). For subjects who are randomized but not dosed after randomization, study day 1 is defined as the date of study randomization.

Study Day

Study day is defined as the number of days from Study Day 1.

- Before Study Day 1: Study Day = (Date of assessment – Date of Study Day 1)
- On or After Study Day 1: Study Day = (Date of assessment – Date of Study Day 1)+1

Therefore, the day prior to Study Day 1 is -1.

Study Randomization

Study randomization is defined as when subject initially receives a random treatment allocation via the IXRS system.

Study Period

Study periods are defined separately for subjects, study eyes, and fellow eyes.

At a subject level:

- Through Week 8:

It is defined as the time period from the first dose of IP the subject received (see definition of first dose date for the subject) to the week 8 dose date (earlier of the dosing dates of the study eye and fellow eye) for subjects who have received week 8 dose, or to the EOS visit for subjects discontinued the study prior to week 8 visit, or to Study Day 64 for subjects who have never received week 8 dose but remained on study. According to the protocol, the treatment of the fellow eye is allowed starting at baseline (day 1) if needed. Subjects are classified according to their randomized treatment at study randomization (aka initial randomized treatment) (ABP 938 or aflibercept) for efficacy analysis. Subjects are classified according to their treatment actually received at the subject level (ABP 938 or aflibercept) for safety and immunogenicity analysis.

- Through Week 16:

It is defined as the time period from the first dose of IP the subject received (see definition of first dose date for the subject) to the 1st dose (earlier of the dosing dates for study eye and fellow eye) post re-randomization for re-randomized and treated subjects, or to the EOS visit for subjects not re-randomized or for subjects who were re-randomized but not treated post re-randomization. For subjects that are ongoing (i.e. EOS visit not available), the analysis data cutoff date will be used. Subjects are classified according to their randomized treatment (ABP 938 or aflibercept) for efficacy analyses. Subjects are classified according to their treatment actually received at the subject level (ABP 938 or aflibercept) for safety and immunogenicity analyses.

- Post Week 16

It is defined as the time period from the first dose (earlier of the dosing dates for study eye and fellow eye) post re-randomization to the EOS visit or analysis data cutoff date, whichever is earlier. Subjects are classified according to their full treatment sequence: ABP 938/ABP 938, aflibercept/aflibercept, or aflibercept/ABP 938. Planned treatment

sequence will be used for efficacy analysis and actual treatment sequence at the subject level will be used for safety and immunogenicity analyses.

- Entire Study

It is defined as the time period throughout the study from the first dose of IP the subject received (see definition of first dose date for the subject) to the EOS visit or analysis data cutoff date, whichever is earlier. Subjects are classified according to their full treatment sequence: ABP 938/ABP 938, aflibercept/aflibercept, or aflibercept/ABP 938. Planned treatment sequence will be used for efficacy analysis and actual treatment sequence at the subject level will be used for safety and immunogenicity analyses.

At an eye level:

The study periods for the study eye and fellow eye are defined based on the first dose and last dose dates of the respective eye. Efficacy analyses will be performed only for the study eye and will be based on the randomized treatment or treatment sequence for the study eye. Safety analyses for study eyes and fellow eyes will be based on actual treatment or treatment sequence received in the respective eye (see the definition of actual treatment in section 5.1).

- Through Week 8:

It is defined as the time period from the first dose of IP of the study eye (fellow eye) to the week 8 dose date of the study eye (fellow eye) for subjects who have received week 8 dose to the study eye (fellow eye), or to the EOS visit for subjects discontinued the study prior to week 8 visit, or to Study Day 64 for subjects who have never received week 8 dose for the study eye (fellow eye) but remained on study. Study eyes (fellow eye) are classified according to treatment actually received by the study eyes (fellow eyes) (ABP 938 or aflibercept) for safety analyses.

- Through Week 16:

It is defined as the time period from the first dose of IP of the study eye (fellow eye) to the first dose of IP of the study eye (fellow eye) post re-randomization for re-randomized and treated subjects or to the EOS visit or for subjects not re-randomized or for subjects who were re-randomized but not treated post re-randomization. For subjects that are ongoing (i.e. EOS visit not available), the analysis data cutoff date will be used. Study eyes (fellow eyes) are classified by the treatment the study eyes (fellow eyes) actually received (ABP 938 or aflibercept) for safety analyses.

- Post Week 16

It is defined as the time period from the first dose of IP of the study eye (fellow eye) post re-randomization to the EOS visit or analysis data cutoff date, whichever is earlier. Study eyes (fellow eyes) are classified according to their full treatment sequence as received (ABP 938/ABP 938, aflibercept/aflibercept, or aflibercept/ABP 938) for safety analyses

- Entire Study

It is defined as the time period throughout the study from the first dose of IP of the study eye (fellow eye) to the subject's EOS visit or analysis data cutoff date, whichever is earlier. Study eyes (fellow eyes) are classified according to their full treatment sequence as received (ABP 938/ABP 938, aflibercept/aflibercept, or aflibercept/ABP 938) for safety analyses.

Study Analysis Visit

Since the actual visit for a subject may not exactly coincide with their scheduled visit date, the actual visit date is mapped to the study analysis visit as follows. The actual visit date is allowed to fall within a specified interval of the target day; this avoids the existence of gaps between weeks.

If more than one actual visit (including the unscheduled visits) falls within the same defined window, the visit closest to the target day with non-missing data will be considered for analysis. If two actual visit dates are at the same distance from the target day, the later visit with non-missing data will be considered for analysis.

For efficacy, intraocular pressure, indirect ophthalmoscopy, slit-lamp:

Study Analysis Visit	Target Day	Study Day	Interval (days)
Baseline	1	≤1	NA
Week 4	29	22-36	15
Week 8	57	50-64	15
Week 16	113	86 – 141	56
Week 24	169	142 – 197	56
Week 32	225	198 – 253	56
Week 40	281	254 - 309	56
Week 48	337	310 - 351	42
Week 52	365	≥352	NA

For vital signs, safety laboratory [a] (including serum chemistry, hematology, urinalysis)

Study Analysis Visit	Target Day	Study Day	Interval (days)
Baseline[b]	1	≤1	NA
Week 8	57	50-64	15
Week 16	113	86 – 141	56

Week 52	365	≥352	NA

[a] Laboratory parameters will only be included at the visits where it is scheduled for assessment in the output tables.

[b] If a subject has laboratory measurements on the same day as the first dose date but at a time after the first dose of IP is administered, the lab measurements will not be defined as baseline, but as week 8 measurements.

The rules above for selecting a visit from multiple ones within the same visit window are not applicable to retest values of lab data. If the lab measurement is a retest, the retest value will be chosen.

For ADA:

Study Analysis Visit	Target Day	Study Day
Baseline	1	≤1
by Week 8	57	≤64
by Week 16	113	≤141
by Week 24	169	≤197
by Week 40	281	≤309
by Week 52	365	NA

For PK substudy:

Nominal visits will be used for PK analysis and analysis windows are not defined for PK visits.

Total IP Exposure Duration

The total IP exposure duration for the subject (in days) for each study period (through week 8, through week 16, post week 16, and entire study) will be derived as: the period end date for the subject – the period start date for the subject +1.

The total IP exposure duration for the study eye (in days) for each study period (through week 8, through week 16, post week 16, and entire study) will be derived as: the period end date for the study eye – the period start date for the study eye +1.

The total IP exposure duration for the fellow eye (in days) for each study period (through week 8, through week 16, post week 16, and entire study) will be derived as: the period end date for the fellow eye – the period start date for the fellow eye+1.

The definitions for each study period at the subject level and eye level are defined in section 5.1.

5.2 Efficacy

Maintaining Vision

A subject is classified as maintaining vision if he/she loses fewer than 15 letters in ETDRS letter score, assessed on the study eyes, compared to baseline.

CNV Area Size and CST

For imaging assessments, when three readers are used, the median value is used for analysis. When two readers are used, the mean value is used for analysis. When only one reader is used then that value is used for analysis.

5.3 Safety

AE Leading to Discontinuation from IP/Study

AEs leading to discontinuation from IP/study are those with an action taken with Investigational Medicinal Product indicating “drug withdrawn” or Other action taken of “study discontinued”.

COVID-19 AEs

COVID-19 AEs will be flagged based on the COVID-19 standardized query (SMQ) of the current MedDRA version at the time of the primary analysis.

Event of Interest (EOI)

An EOI is defined as a noteworthy event for a particular product or class of products that a sponsor may wish to monitor carefully. It could be serious or non-serious and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals (Council for International Organizations of Medical Sciences [CIOMS] VI, 2005). The EOIs for this study will include:

- Endophthalmitis
- Retinal Detachment
- Increase in Intraocular Pressure
- Thromboembolic events

The detailed search strategies for the EOIs are included in Appendix 1.

Treatment-emergent Adverse Event

A treatment-emergent AE (TEAE) for subjects, study eye, and fellow eye is defined for each study periods, when applicable.

A treatment-emergent AE (TEAE) for a given study period is defined as an AE that begins in the respective study period (see definition of Study Period in section 5.1).

If the AE starts on the same day as the first dose of IP then the flag indicating whether the AE started prior to the first dose on the adverse event CRF page will be used. For re-randomized and treated subjects, an AE that starts on the same day as the first dose post re-randomization will be considered as a TEAE post week 16.

Ocular AEs that occur in the fellow eye prior to fellow eye treatment are considered treatment-emergent at the subject level but will not be considered treatment-emergent for fellow eye.

6. Analysis Sets

6.1 Full Analysis Set

The Full Analysis Set (FAS) will include all randomized subjects. It will be analyzed according to randomized treatment (regardless of actual treatment received). This analysis set will be the primary set used for analyses/summaries of the primary efficacy endpoint, as well as for all secondary efficacy endpoints.

6.2 Safety Analysis Set

The Safety Analysis Set will include all subjects who receive at least one dose of IP. It will be analyzed according to actual treatment received. This analysis set will be used for summaries of safety data as well as immunogenicity data.

6.3 Per Protocol Set(s)

The Per protocol (PP) Analysis Set will include all subjects in the FAS who have completed dosing at day 1 and week 4 and have completed BCVA assessment at week 8 without experiencing an important protocol deviation that may affect their evaluation for the primary endpoint of the study. Important protocol deviations that could affect the primary endpoint will be defined and agreed upon before unmasking for the primary analysis. This analysis set will be used for sensitivity analyses for the primary and key secondary efficacy endpoints. Analyses will be based on actual treatment the subject received in the study eye (see definition of actual treatment received at the study eye level in section 5.1).

6.4 Pharmacokinetic (PK) Analysis Set

The PK Analysis Set will include all subjects enrolled in the PK substudy who receive at least one dose of IP between day 1 and week 8 (inclusive) and who have at least 1 reported serum concentration of ABP 938 or aflibercept. The analysis set will be analyzed according to actual treatment the subject received in the study eye (see definition of actual treatment received at the study eye level in section 5.1).

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

No interim analyses are planned for this study.

7.2 Primary Analysis

The primary analysis (PA) for the study will be performed after all subjects reach week 24 or terminate early, and the analysis will comprise at least 24 weeks of efficacy, safety, and immunogenicity data.

All data collected by the time of data cut will be included in the PA. An independent unmasked team who are not involved in the operations of the study after PA database lock will perform the PA.

7.3 Final Analysis

The final analysis will be performed at the end of study after all enrolled subjects have completed week 52 visit (or early terminated from the study).

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

Data screening process will be documented in a data management plan by Parexel and agreed by Amgen. In addition to the data screening built into the Parexel Data Management Plan, the programming of analysis datasets, tables, figures and listings (TFL) provides additional data screening.

When the database has been declared to be complete and accurate, the database will be locked. Database lock will follow the standard operating procedure(s) at Parexel.

8.2 Data Handling and Electronic Transfer of Data

Clinical data will be entered in RAVE database and exported as SAS® version 9.4 or higher datasets. Converted datasets will be created using SAS® and following standard Clinical Data Interchange Standards Consortium Standard Data Tabulation Model (CDISC SDTM, version 1.4, Implementation Guide version v3.2) conventions. Analysis datasets will be created using SAS® and following CDISC Analysis Data Model (ADaM, version 2.1, Implementation Guide 1.1) standards.

Medical history and AEs will be coded using the current version of MedDRA at the time of the primary analysis to assign a system organ class (SOC) and preferred term (PT) to each event. Adverse events and abnormal laboratory results considered as AEs are

assigned a toxicity grade according to National Cancer Institute (NCI-US) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Prior and concomitant medications will be coded using the current version of the World Health Organization Drug Dictionary (WHO-DD) at the time of the primary analysis.

8.3 Handling of Missing and Incomplete Data

For both the primary and secondary efficacy endpoints, the primary analysis will be based on observed data and FAS; missing values will not be imputed. As a sensitivity analysis, missing data will be imputed by LOCF for the primary endpoint and NRI for the binary secondary endpoints. In addition, for the primary endpoint, tipping point analyses and a repeated-measures analysis will be performed to explore the sensitivity of the results based on different assumptions for the missing data.

Missing safety and PK endpoints will not be imputed.

Imputation for Partial or Missing Dates

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

Table 2: Imputation Rules for Partial or Missing Start Dates

Start Date		Stop Date						
		Complete: yyyymmdd		Partial: yyyymm		Partial: yyyy		Missing
		<1st dose	≥1st dose	<1st dose yyyymm	≥1st dose yyyymm	<1st dose yyyy	≥1st dose yyyy	
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 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.

8.4 Validation of Statistical Analyses

All report outputs will be produced/All statistical analyses will be performed using SAS® version 9.4 or a higher version in a secure and validated environment.

Programs will be developed and maintained and output will be verified in accordance with current standard operating procedures at Parexel. The validation process is repeated any time TFLs are re-delivered with different data. Execution of this validation process is documented throughout the study. The entire set of TFLs will be checked for completeness, accuracy prior to its delivery to Amgen.

9. Statistical Methods of Analysis

9.1 General Considerations

All statistical analyses will be performed using SAS® (Version 9.4 or higher).

Unless otherwise specified, descriptive data summaries will be tabulated by treatment for all endpoints. Categorical data will be summarized using number of subjects,

frequency and percentages of subjects falling into each category, with the denominator for percentages being the number of subjects in the analysis sets for each treatment group, unless otherwise noted. Percentages will be rounded to one decimal place except for 100%, which will have no decimal place.

All continuous variables will be summarized using mean, standard deviation, median, minimum, maximum, 25th percentile (Q1), 75th percentile (Q3), and number of subjects with observations. The mean, median, Q1, and Q3 will be presented to one decimal place greater than the original data, standard deviation will be to two decimal places greater than the original data, and the minimum and maximum will have the same number of decimal places as the original data.

Confidence intervals (CIs) may also be provided (when specified).

For any of the summaries that are to be done by visit, the derived analysis study visit as defined in Section 5.1 will be used for analysis unless otherwise noted.

9.2 Subject Accountability

The following information will be summarized for subject disposition and accountability:

- Number of subjects randomized at the initial randomization (2 treatment groups) and re-randomization (3 treatment sequences) by geographic region, country, and site.
- Subject disposition before and after re-randomization (including number of subjects who were randomized, treated with ABP 938/aflibercept in study eye and fellow eye, completed IP in study eye, discontinued IP in study eye and fellow eye with reason of discontinuation, completed study and discontinued study with reason of discontinuation) for each of the analysis sets defined in Section 6. Note that discontinued IP and discontinued study due to COVID-19 related reasons will be further summarized by Adverse Event or “Other”.
- Number of screened subjects and number of subjects in each analysis set by initial randomized treatment, and reasons for exclusion from each analysis set.
- Randomization list of subjects and their actual versus randomized and/or re-randomized treatment groups for all randomized subjects.

9.3 Important and COVID-19 Related Protocol Deviations

Important Protocol Deviations (IPDs) data will be identified and recorded. The study team will conduct on-going reviews of the IPD data throughout the study and the

resulting set of subjects to be included in the PP analysis set. The PP analysis set must be finalized prior to database lock of each analysis.

A summary of incidence of IPDs will be tabulated using number and percentage of subjects by deviation type (including COVID-19 related) and initial randomized treatment through week 16 and by initial/re-randomized treatment through entire study. In addition, a summary of incidence of any eligibility related PDs (regardless of important or not important) will be tabulated using number and percentage of subjects by deviation type and initial randomized treatment. Listings of subjects with IPDs will be provided to support these summary tables (with a flag indicating whether the deviation leads to exclusion from the PP analysis set, and another flag indicating if COVID-19 related in all listings). A subject listing with eligibility criteria deviations will also be provided.

Furthermore, all COVID-19 related protocol deviations (PD) will be summarized by COVID-19 related deviation type for the FAS through week 16 and entire study. Listings of subjects with COVID-19 related PDs will be provided to support these summary tables.

9.4 Demographic and Baseline Characteristics

The following demographics and baseline characteristics will be summarized by treatment for the FAS, PP analysis set, and safety analysis set and by treatment sequence for the subset of subjects in the FAS who are re-randomized and for the subset of subjects in the safety analysis set who are re-randomized and treated post re-randomization:

- age (in years, at time of signing informed consent) and age category (< 65 vs ≥ 65),
- race,
- sex,
- ethnicity,
- height,
- weight,
- body mass index (BMI),
- geographic region,
- duration of disease (in weeks),
- baseline BCVA group (≤ 64 vs > 64 letters),
- BCVA ETDRS letter score,
- CNV area size,

- CST

9.5 Efficacy Analyses

Efficacy analyses will be performed for the study eye and will be based on the randomized treatment or treatment sequence for the study eye.

9.5.1 Analyses of Primary Efficacy Endpoint/Estimand

The primary estimand is the difference in change from baseline in BCVA at week 8 between the ABP 938 group and the aflibercept group in subjects with neovascular (wet) AMD who are randomized, regardless of missing or discontinuing investigational product administration to the study eye, or use of additional medications for AMD in the study eye prior to observing BCVA at week 8.

The intercurrent events will be handled using a treatment policy strategy. The value of BCVA at week 8 (if observed) will be used regardless of whether an intercurrent event occurs. Missing BCVA value at week 8 is assumed to be missing completely at random (MCAR) for the primary analysis for the primary estimand based on observed data using the FAS.

The primary efficacy endpoint is change from baseline in BCVA as measured by ETDRS letter score at week 8.

9.5.1.1 Primary Analysis

The primary analysis will be performed using the FAS based on randomized treatment and observed data.

Analysis will assess the hypothesis that there are no clinically meaningful differences between ABP 938 and aflibercept treatment arms in BCVA change from baseline at week 8. The clinical similarity will be evaluated by comparing the 2-sided 95% CI of the change from baseline at week 8 of BCVA between ABP 938 and aflibercept arms with an equivalence margin of (-3.9, 3.9) (global). If the 2-sided 95% CI is within the pre-specified global equivalence margin (-3.9, 3.9), then it is declared that ABP 938 and aflibercept is clinically similar per global criteria. For the US BLA submission, the clinical similarity will be evaluated by comparing the 2-sided 90% CI (rounding to the nearest integers) of the change from baseline at week 8 of BCVA between ABP 938 and aflibercept arms with an equivalence margin of (-3, 3). The point estimate of the mean difference in change from baseline in BCVA at week 8 between ABP 938 and aflibercept and its corresponding 2-sided 90% and 95% confidence intervals will be obtained from

an ANCOVA model with treatment, region and baseline BCVA measurement as covariates. Regions with small number of subjects in them will be combined.

9.5.1.2 Sensitivity Analyses

To assess the robustness of the primary analysis result, the ANCOVA analysis described above will be repeated using the PP analysis set based on observed cases and using FAS analysis set based on LOCF imputation.

In addition, a repeated-measures analysis for day 1 through week 8 period based on FAS analysis set will be performed as a sensitivity analysis. Besides the stratification factor of region, the baseline BCVA value, visit, treatment, and treatment-by-visit interaction will be included in the model, with visit as a categorical variable. The point estimate of the mean difference in change from baseline in BCVA at week 8 between ABP 938 and aflibercept and its corresponding 2-sided 90% and 95% confidence intervals will be obtained. The mixed model repeated measures analysis will be implemented using PROC MIXED and a compound symmetry covariance structure in SAS.

Another sensitivity analysis based on FAS will be done to explore the impact of the baseline covariates in section 9.4 on BCVA change from baseline at week 8 in addition to the stratification factor of region and the baseline BCVA value. A stepwise model selection (with <0.25 p-value to enter the model and <0.1 to stay in the model) will be fit using PROC GLM and will be used to determine if any of the covariates have significant impact on the outcome variable. The final ANCOVA model will be fit using PROC GLM and will maintain treatment, the stratification factor region, the baseline BCVA value, and the covariates identified by the stepwise model.

In addition, the mean difference in the BCVA change from baseline at week 8 between the two group will be examined in the subgroups as defined by the covariates in Section 4.1. These additional explorations will be performed on the FAS by using the ANCOVA analysis. The 90% CI and 95% CIs of difference in mean change from baseline of BCVA across these subgroups will be displayed by forest plots.

The rate of missing BCVA at week 8 will be tabulated with reasons, such as missing baseline, outside of the defined week 8 analysis time frame and discontinued from the study early prior to week 8 (i.e. prior to day 50).

Tipping point analyses will be performed using FAS to explore the sensitivity of results to violations in assumptions about the missing data (i.e., to various missing not-at-random

assumptions). Assumptions (tipping point) under which the 90% CI or 95% CI no longer rules out unacceptable differences in efficacy as determined by BCVA change from baseline at week 8 between ABP 938 and aflibercept will be identified.

In this analysis, all the observed data will be included as non-missing, regardless of adherence to treatment or use of prohibited medication. The analysis will be performed using a general three-step approach:

(1) Multiple imputation will be done using PROC MI to generate multiple (e.g., 10) imputed datasets by imputing missing data assuming monotone missing pattern and that subjects with missing data have, on average, worse or better efficacy compared to those who have values. The mean difference between the (unobserved) missing values and observed values (refer to as shift) can vary independently for the different treatment groups.

(2) Each of these imputed datasets (which contains identical values of non-missing data but different values imputed for missing data) is analyzed using standard SAS procedure, e.g., PROC GLM, PROC GENMOD, etc.

(3) Results from all imputed datasets are then combined together for overall inference using PROC MIANALYZE.

For BCVA change from baseline at week 8, seven equally spaced shifts (-6 to 6 by 2) for the BCVA change from baseline for subjects with missing data will be explored.

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

Analyses for secondary efficacy endpoints will be provided by visit from Day 1 to EOS. In general, treatment comparison of interest for time points prior to re-randomization (week 16 included) include the comparison between treatment ABP 938 and aflibercept; treatment comparison of interest for time points after re-randomization include the comparison between treatment sequence ABP 938/ABP 938 and aflibercept/aflibercept and the comparison between treatment sequence aflibercept/ABP 938 and aflibercept/aflibercept. Analysis strata with small number of subjects in them will be combined.

9.5.2.1 Proportion of subjects who maintained vision at week 52

The analyses of proportion of subjects who maintained vision are descriptive and will be based on observed cases and FAS.

The number and percent of subjects who maintained vision at week 52 with the associated 95% CI will be summarized by initial/re-randomization treatment sequence. In addition, treatment risk difference and the corresponding 90% and 95% CI will be estimated using the stratified Newcombe confidence limits (with Mantel-Haenszel weights) adjusting for stratification factors. In addition, the above analyses for proportion of subjects who maintained vision will be repeated using NRI for FAS.

9.5.2.2 Proportion of subjects who gained ≥ 15 letters at week 52

The analyses of proportion of subjects who gained ≥ 15 letters will be performed per the analyses for the proportion of subjects who maintained vision at week 52 (as described in section 9.5.2.1).

9.5.2.3 Proportion of subjects who gained ≥ 10 letters at week 8

The analyses of proportion of subjects who gained ≥ 10 letters will be performed per the analyses for the proportion of subjects who maintained vision at week 52 (as described in section 9.5.2.1). The analysis will be repeated using PP analysis set.

9.5.2.4 Change from baseline in BCVA over the study duration

For time period from Day 1 to EOS, change from baseline in BCVA as measured by ETDRS letter score at each visit will be analyzed using the same ANCOVA model for primary analysis as described in section 9.5.1.1 for the FAS and observed cases.

The BCVA change from baseline will be plotted by treatment and visit for the FAS with mean and 95% CI.

9.5.2.5 Change from baseline in CNV area size and CST over the study duration

The analyses of CNV area size and CST are descriptive. For time period from Day 1 to EOS, change from baseline in CNV area size and CST at each visit will be analyzed using an ANCOVA model with baseline CNV area size or CST measurement and stratification factors as covariates for the FAS and observed cases. Treatment difference and 90% and 95% CI will be estimated.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

The number and percent of subjects who maintained vision at each visit along with the associated 95% CIs will be summarized and plotted by initial randomized treatment for all subjects in the FAS through week 16 and by initial/re-randomization treatment sequence for re-randomized subjects post week 16 through EOS using the observed data.

Proportion of subjects who gained ≥ 10 letters and ≥ 15 letters at each visit will be summarized similarly.

9.6 Safety Analyses

All safety analyses will be performed on the safety analysis set based on actual treatment received (see definitions of actual treatment in Section 5.1).

Subject level and study eye level safety summaries will be provided separately as follows:

- through week 8 period for the actual treatment groups: ABP 938 and aflibercept.
- through week 16 period for the actual treatment groups: ABP 938 and aflibercept.
- post week 16 period for the actual treatment sequence: aflibercept/aflibercept and aflibercept/ABP 938, and ABP 938/ABP 938.
- entire study period for the actual treatment sequence: aflibercept/aflibercept and aflibercept/ABP 938, and ABP 938/ABP 938.

The definitions for each study period at subject level and for the study eye are provided in Section 5.1.

For the subset of subjects who also have the fellow eye treated with the IP, their safety data collected for the fellow eye from the first IP treatment of the fellow eye to the EOS visit will be summarized similarly. Summaries will be based on the actual treatment received in the fellow eye (see definition in Section 5.1).

9.6.1 Adverse Events

All reported AEs will be coded to the appropriate SOC and PT according to the most current version of MedDRA at the time of the primary analysis, and the severity of each AE will be graded by the investigator per CTCAE v4.03 criteria.

<u>At the subject level:</u>

For summary of AEs at the subject level, the following AE summaries, (a) through (h), will be provided by treatment for each study period of through week 8, through week 16, and post week 16. In addition, summaries (a) and (c) will be provided for the entire study period.

(a) overall summary of treatment-emergent AEs,

(b) treatment-emergent AEs by SOC, PT, and maximum severity grade,

(c) treatment-emergent AEs by SOC and PT,

(d) overall summary of treatment-emergent EOIs,

(e) treatment-emergent AEs by PT,

(f) grade 3 or higher treatment-emergent AEs by PT,

(g) treatment-emergent AEs leading to discontinuation from IP/study by PT,

(h) treatment-emergent EOIs by PT,

(i) treatment-emergent COVID-19 AEs by PT,

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

AEs tabulated by preferred term will be presented in descending order of frequency in the ABP 938 arm or the ABP 938/ABP 938 arm when appropriate.

The risk difference and 95% CI of each EOI through week 8, through week 16 and post week 16 will be calculated on the safety analysis set using Wald asymptotic confidence limits or exact confidence limits (Farrington-Manning score) if the number of subjects with EOIs for any treatment is less than 25. Forest plots will be created to summarize the variability in risk difference across the EOIs.

Listings of treatment-emergent EOIs from day 1 through the EOS visit will be provided.

<u>At the eye level:</u>

For summary of AEs of study eyes or fellow eyes, the following summaries will be provided by treatment for through week 8, through week 16, and by treatment sequence post week 16.(refer to definitions of study period in Section **Error! Reference source not found.**):

- overall summary of ocular treatment-emergent AEs, including serious AE summary by serious criteria,
- treatment-emergent ocular AEs by SOC, PT, and maximum severity grade,
- treatment-emergent ocular AEs by SOC and PT,
- treatment-emergent Ocular AE Leading to Discontinuation From IP or Study by PT,
- treatment-emergent intraocular inflammation Events by PT,
- treatment-emergent vitreous hemorrhage Events by PT.

Searching strategies of AEs intraocular inflammation and vitreous hemorrhage are specified in Appendix 2 Search strategy of INTRAOCULAR INFLAMMATION and VITREOUS HAEMORRHAGE.For the entire study period, the following summaries will be provided.

- overall summary of ocular treatment-emergent AEs, including serious AE summary by serious criteria,
- treatment-emergent ocular AEs by SOC and PT,

Counting of AEs will be by respective eye within subject and will be counted only once within each SOC or PT by study period. For tables categorized by severity, study eyes or fellow eyes with multiple events within a particular SOC or preferred term will be counted under the category of their most severe event with that SOC or preferred term for the respective eyes.

In addition, a listing of ocular AEs for study eyes and fellow eyes from day 1 through the EOS visit will be provided.

9.6.2 Deaths and Serious Adverse Events

Summaries of serious treatment-emergent AE will be provided for subjects, study eyes and fellow eyes by study periods, except for the entire study period. Death summary will only be provided at the subject level by study periods, except for the entire study period.

At the subject level:

Subject incidence of the following will be tabulated for study period: through week 8, through week 16, and post week 16:

(j) serious treatment-emergent AEs by SOC and PT,

(k) serious treatment-emergent AEs by PT,

(l) treatment-emergent fatal AEs by PT.

(m) serious treatment-emergent AEs occurring on or after presumed start date of COVID-19 infection by PT.

Summaries will be sorted in descending order of frequency in the ABP 938 arm or ABP 938/ABP938, when applicable.

Refer to counting AE for the subject level analysis in section 9.6.1.

A listing of treatment-emergent serious AEs and a listing of treatment-emergent serious AEs occurring on or after presumed start date of COVID-19 infection from day 1 through EOS visit will be provided.

At the eye level:

Treatment-emergent serious AEs by treatment groups and by PT will be summarized for study period: through week 8, through week 16, post week 16 for the study eyes and fellow eyes. (refer to counting AE for the eye level analysis in section 9.6.1).

9.6.3 Laboratory Test Results

Laboratory data (hematology, serum chemistry, and urinalysis) will be converted to Système International units for reporting and processing purposes. Absolute values and changes from baseline by visit will be presented descriptively for each study period except for through week 8 period (refer to study period definition in section 5.1). Shift tables of the worst on-study laboratory toxicity based on CTCAE grading relative to baseline will be presented by study period. There is no re-baseline for post week 16 analyses.

The shift tables will take into account all post-baseline (schedule and unscheduled) laboratory results in the determination of the worst on-study laboratory toxicity. In addition, subject incidence tables of grade ≥ 3 laboratory toxicities will be provided. Standard ranges will be used for the laboratory analysis.

Lab assessments will be grouped for summary as follows:

Hematology: hemoglobin, hematocrit, red blood cells, platelets, total white blood cell (WBC) count, differential WBC count, and absolute neutrophil count

Biochemistry: albumin, alkaline phosphatase, alanine aminotransferase (ALT), amylase, aspartate aminotransferase (AST), calcium, creatinine, gamma glutamyltransferase, glucose, lipase, potassium, sodium, and total bilirubin

Urinalysis: pH, specific gravity, creatinine, glucose, bilirubin, blood, and protein

9.6.4 Vital Signs

Observed and change from baseline for each vital sign parameter will be summarized descriptively by visit for study periods: through week 16, post week 16, and the entire study (refer to study period definition in section 5.1 and treatment group/sequence specified for subject level safety summary in section 9.6).

9.6.5 Intraocular Pressure

Observed and change from baseline for intraocular pressure for the study eyes and fellow eyes will be summarized by visit and time point for the following study periods: through week 16, post week 16, and the entire study (refer to study period definition in section 5.1 and treatment group/sequence specified for eye level safety summary in section 9.6).

9.6.6 Slit-Lamp Examination and Indirect Ophthalmoscopy

Abnormal slit-lamp biomicroscopy and indirect ophthalmoscopy results for the study eyes and fellow eyes will be summarized by visit and time point for study periods: through week 16, post week 16, and entire study (refer to study period definition in section 5.1 and treatment group/sequence specified for eye level safety summary in section 9.6).

9.6.7 Physical Examinations

None.

9.6.8 Immunogenicity

The number and percentage of subjects developing binding ADAs will be tabulated by visit and actual treatment received at a subject level (refer to definition of actual treatment received in section 5.1).

Developing antibody incidence through week 16 and through EOS is defined as the number of subjects with a negative or no antibody result at baseline and a positive antibody result at a post-baseline visit divided by the number of subjects with a binding negative or no result at baseline and at least one post baseline result within the respective study period. Treatment boosted ADA is defined as total number and percentage of subjects with a positive immunoassay result at baseline and at least 1 post-baseline immunoassay result that is ≥4x magnitude of baseline result. A transient antibody result is defined as a positive post-baseline result with a negative result at the subject's last visit tested within the respective study period.

Developing antibody incidence in the post week 16 period is evaluated among subjects who were re-randomized and treated post re-randomization. It is defined as number of subjects who had a positive result post re-randomization, had never tested positive (i.e., negative or no results) through week 16, and tested negative at the last visit prior to receiving IP post re-randomization by the number of subjects who had at least a result post re-randomization, had never tested positive (i.e., negative or no results) through

week 16, and tested negative at the last visit prior to receiving treatment post re-randomization.

9.6.9 Exposure to Investigational Product

IP exposure (ABP 938 or aflibercept) will be tabulated separately for subject, the study eye and the fellow eye using the safety analysis set and according to the actual treatment received. Summary statistics will be provided for the total number of doses administered, total dose received, and total duration of IP exposure by the different study periods specified for the safety analyses in section 9.6.1. For study eyes and fellow eyes, the number of subjects who missed at least one dose of IP due to COVID-19 related reasons will be summarized by number of doses not administered. In addition, the number of subjects with at least one dose not administered will be summarized by reason and also by relatedness to COVID-19.

A subject listing of each administered lot number(s) for IP and a listing of unique manufacturing lot numbers used in the study will be provided separately for subject, the study eye and the fellow eye.

9.6.10 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the current version of the World Health Organization-Drug Dictionary (WHO-DD) and will be summarized by preferred name. The prior medications will be summarized by initial treatment the subject received. The concomitant medications will be summarized for the different study periods specified for the safety analyses in section 9.6.1 using safety analysis set.

The number and percentage of subjects using each medication will be displayed by treatment arm. Subjects taking more than one medication in the same preferred name will be counted once for the number of subjects taking that preferred name.

9.7 Other Analyses

9.7.1 Analyses of Pharmacokinetic Endpoints

Serum ABP 938 and aflibercept concentrations from the PK substudy will be summarized descriptively by treatment for each sampling time point for PK analysis set.

9.7.2 Analyses of Clinical Outcome Assessments

None.

9.7.3 Analyses of Health Economic Endpoints

None.

9.7.4 Analyses of Biomarker Endpoints

None.

10. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

11. Literature Citations / References

1. Ke C, Wang J, Zhang C, Jiang Q, Snapinn S. On errors in stratified randomization. Statistics in Biopharmaceutical Research 2017; 9 (2): 225-33.
2. US FDA. Guidance for Industry: Scientific considerations in demonstrating biosimilarity to a reference product. April 2015a, US FDA.

Appendix 1 List of Events of Interest and the Associated SMQ and EOI Searching Strategies

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)

Appendix 2 Search strategy 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*