CLINICAL STUDY 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
Protocol number:	20170542
Study phase:	Phase 3
Test product:	ABP 938
Regulatory agency identifier number(s):	IND number 135489 EudraCT number 2019-002503-17
Sponsor:	Amgen, Inc One Amgen Center Drive Thousand Oaks, CA USA 91320
Contract research organization:	Parexel International (IRL) Limited
Protocol version and date:	Version **4.0**, **16 May 2022**

This study will be performed in compliance with the principles of Good Clinical Practice.

NCT Number: NCT04270747
This NCT number has been applied to the document
for purposes of posting on Clinicaltrials.gov

PROTOCOL SIGNATURE PAGE – SPONSOR

This protocol has been reviewed and approved by the representative(s) listed below. Any modification of the protocol must be agreed upon by the sponsor and the investigator and must be documented in writing.

Amgen, Inc representative(s):

[redacted]

Print Name Title

[redacted]

Signature Date (DD Month YYYY)

PROTOCOL SIGNATURE PAGE – CONTRACT RESEARCH ORGANIZATION (CRO)

This protocol has been reviewed and approved by the representative(s) listed below. Any modification of the protocol must be agreed upon by the sponsor and the investigator and must be documented in writing.

CRO representative(s):

[redacted]

Print Name Title

[redacted]

S[redacted] Date (DD Month YYYY)

PROTOCOL SIGNATURE PAGE – INVESTIGATOR

I have read this protocol, which has been agreed by Amgen, Inc and given approval/favorable opinion by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and I agree that it contains all necessary details for my staff and I to conduct this study as described. I will provide copies of the protocol and any amendments to all study personnel under my supervision and provide access to all information provided by Amgen, Inc or their specified designees. I will discuss the material with the study personnel to ensure that they are fully informed about the study.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from Amgen, Inc. It is, however, permissible to provide information to a subject (or a legally authorized representative) in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the general guidelines indicated in the Declaration of Helsinki, International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), and applicable national or regional regulatory requirements.

I agree to comply with the procedures described for data recording and reporting and to permit monitoring and auditing by Amgen, Inc, and inspection by the appropriate regulatory authorities.

I agree to make my subjects' study records available to Amgen, Inc personnel, their representatives and relevant regulatory authorities in order to verify data that I have entered into the case report forms. I will retain the study-related essential documents until Amgen, Inc indicates that they are no longer needed. I am aware of my responsibilities as an investigator as provided by Amgen, Inc.

I agree to ensure that Financial Disclosure Statements will be completed by me (including, if applicable, my spouse [or legal partner] and dependent children) and my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children) at the start

of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I understand that Amgen, Inc may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to Amgen, Inc.

Investigator:

Print Name	Title

Institution

Signature	Date (DD Month YYYY)

SERIOUS ADVERSE EVENT CONTACT INFORMATION

Serious adverse event information will be recorded in the electronic data capture (EDC) system and transmitted to Amgen within 24 hours following the investigator's knowledge of the event. If the EDC system is not functional, the serious adverse event can be reported by faxing a completed paper Serious Adverse Event Form or by direct telephone communication with Parexel at the numbers provided below. The event must be updated electronically in the EDC system by the clinical study center once the EDC function resumes.

Global reporting of SAEs (except Japan):

Phone (Safety line): +1 (781) 434-5010

NorthAmerica_Medical@parexel.com

Japan (Safety line): +81 3 6888 5377

PROTOCOL AMENDMENT 3 (16 MAY 2022)

Amendment rationale

In accordance with the International Council for Harmonisation (ICH) E9 (R1) addendum, the protocol is amended to specify the primary estimand of the study and to update the statistical section of the protocol in order to meet the regulation obligation for the USA Food and Drug Administration.

All content updates to the existing text in this protocol amendment are illustrated throughout in BOLD font and presented in this protocol summary.

Changes from the protocol version 3.0 to protocol version 4.0

- **Footnotes "b, d, g, j" of Table 1 Schedule of Activities have been updated.**
- **Objectives/Endpoints/Estimand in the Protocol Summary has been updated to include the information of primary estimand.**
- **Statistical methods in the Protocol Summary has been updated.**
- **Section 2 Study Objectives, Endpoints, and Estimand has been updated to include the information of primary estimand.**
- **Section 8.5.1 Primary Endpoint/Estimand has been updated to include the analysis of primary estimand.**
- **Section 8.5.10 Handling of Missing Values has been updated to further clarify the analysis of missing data.**
- **Section 17.1 Sponsor's medical expert and clinical research organization's medical monitor information have been updated.**

PROTOCOL SUMMARY

Protocol number: 20170542

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

Sponsor: Amgen, Inc

Study phase: Phase 3

Indication: Neovascular Age-related Macular Degeneration

Study centers: Approximately 126 global sites

Objectives/Endpoints/Estimand:

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 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 (ADA)

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.

Study design: This is a randomized, double-masked, active controlled multiregional clinical study in adult subjects with neovascular (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 (ie, 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 EOS visit will be conducted at week 52 for subjects that complete the study.

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 terminate early. An external, independent data monitoring committee will evaluate the safety data throughout the study.

For subjects receiving neovascular (wet) AMD treatment in the fellow eye during the study, sites must request an additional box of investigational product.

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 (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.

Study procedures: Efficacy procedures will include BCVA, recorded using ETDRS charts, FA, and SD-OCT. Safety procedures will include assessment of adverse events, clinical laboratory tests, vital signs, indirect ophthalmoscopy, slit-lamp test, and intraocular pressure.

Study duration: After a screening period of up to 4 weeks, subjects will receive investigational product for 48 weeks, followed by a safety follow-up period to week 52, for a total study duration of up to 56 weeks. The start of the study will be the date on which the first subject is randomized to the study, and the end of the study will be the last subject's last assessment.

Planned number of subjects: Approximately 566 subjects (including at least 30 subjects from East Asia) will be randomized in a 1:1 ratio to receive ABP 938 (Treatment Group A) or aflibercept (Treatment Group B). The total sample size will provide approximately 90% power to demonstrate equivalence at a 2-sided significance level of 0.025 with an equivalence margin of (-3.9, 3.9) on the primary efficacy endpoint of 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. In addition, the number of East Asian subjects (ie, 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.

Target population:

Both eyes will be assessed at the screening visit for eligibility, and only 1 eye will be selected from each subject as the study eye. In case both eyes meet the eligibility criteria, the study eye will be the one with the worst BCVA. All images will be sent to central imaging vendor for confirming eligibility.

INCLUSION CRITERIA:

1. Subjects or their legally authorized representative must sign an Institutional Review Board/Independent Ethics Committee approved informed consent form before any study-specific procedures
2. Men or women ≥ 50 years old
3. Subjects must be diagnosed with neovascular (wet) AMD in the study eye (confirmed by central imaging vendor before randomization)
4. Active, treatment naïve subfoveal CNV lesions secondary to neovascular (wet) AMD including juxtafoveal lesions that affect the fovea as confirmed with SD-OCT, FA and/or FP in the study eye (confirmed by central imaging vendor before randomization)
5. BCVA between 73 and 34 letters, inclusive, in the study eye using ETDRS testing
6. Presence of intra and/or subretinal fluid as identified by SD-OCT attributable to active CNV in the study eye (confirmed by central imaging vendor before randomization)

7. Central retinal thickness of > 270 µm in the study eye as measured by the machine calculated average thickness in the ETDRS central 1 mm subfield (CST) by SD-OCT at screening (confirmed by central imaging vendor before randomization)

EXCLUSION CRITERIA:

Eye Related

Subjects are excluded if they meet any of the following criteria in the study eye:

1. Total lesion size > 12 disc areas (30.5 mm^2, including blood, scars, and neovascularization) in the study eye (confirmed by central imaging vendor before randomization)
2. Active CNV area (classic plus occult components) that is < 50% of the total lesion area in the study eye (confirmed by central imaging vendor before randomization)
3. Scar, fibrosis, or atrophy involving the center of the fovea in the study eye (confirmed by central imaging vendor before randomization)
4. Presence of retinal pigment epithelium tears or rips involving the macula in the study eye (confirmed by central imaging vendor before randomization**)**
5. History of any vitreous hemorrhage within 4 weeks before randomization in the study eye
6. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of 8 diopters or more negative or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye (confirmed by central imaging vendor before randomization with the exception of the refractive error and axial length which is to be assessed by the investigator)
7. Prior vitrectomy or laser surgery of the macula (including photodynamic therapy or focal laser photocoagulation) in the study eye
8. History of retinal detachment in the study eye
9. Any history of macular hole of stage 2 and above in the study eye
10. Any macular pathology that might limit vision i.e., Vitreomacular traction or significant epiretinal membrane (confirmed by central imaging vendor before randomization) in the study eye
11. Any intraocular or periocular surgery within 3 months before randomization on the study eye, except lid surgery, which may not have taken place within 4 weeks before randomization, as long as it is unlikely to interfere with the injection
12. Prior trabeculectomy or other filtration surgery in the study eye
13. Uncontrolled glaucoma (defined as intraocular pressure ≥ 25 mmHg despite treatment with antiglaucoma medication) in the study eye
14. Aphakia or pseudophakia with complete absence of posterior capsule (unless it occurred as a result of a yttrium aluminum garnet [YAG] posterior capsulotomy) in the study eye
15. Previous therapeutic radiation in the region of the study eye
16. History of corneal transplant or corneal dystrophy in the study eye
17. Significant media opacities, including cataract, which might interfere with visual acuity or assessment of safety, in the study eye

18. Any concurrent intraocular condition other than neovascular (wet) AMD in the study eye that, in the opinion of the investigator, requires planned medical or surgical intervention during the study or increases the risk to the subject beyond what is expected from standard procedures of intraocular injection, or which otherwise may interfere with the injection procedure or with evaluation of efficacy or safety

Subjects are excluded if they meet any of the following criteria in either eye:

19. History or clinical evidence of uveitis, diabetic retinopathy, diabetic macular edema, or any other vascular disease affecting the retina, other than neovascular (wet) AMD (confirmed by central imaging vendor before randomization)
20. Active intraocular inflammation or active or suspected ocular or periocular infection, within 2 weeks before randomization
21. Active scleritis or episcleritis or presence of scleromalacia

Other Medical Conditions

22. Active extraocular infection or history of extraocular infections as follows:
    a. any active infection for which systemic anti-infectives were used within 4 weeks before randomization
    b. recurrent or chronic infections or other active infection that, in the opinion of the investigator, might cause this study to be detrimental to the subject
23. Acute coronary event or stroke within 3 months before randomization
24. Uncontrolled, clinically significant systemic disease such as diabetes mellitus, hypertension, cardiovascular disease including moderate to severe heart failure (New York Heart Association class III/IV), renal disease, or liver disease
25. Malignancy within 5 years EXCEPT treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, OR in situ breast ductal carcinoma

Washouts and Nonpermitted Treatments

26. Any prior ocular or systemic treatment, including another investigational product or surgery for neovascular (wet) AMD (including anti-vascular endothelial growth factor [VEGF] therapy) in the study eye, except dietary supplements or vitamins
27. Any ocular or systemic treatment including another investigational product or surgery for neovascular (wet) AMD (including anti-VEGF therapy) in the fellow eye, within 30 days before randomization, except dietary supplements or vitamins
28. Prior systemic anti-VEGF treatment as follows:
    a. Investigational or approved anti-VEGF therapy systemically within 3 months before randomization
    b. Aflibercept, ziv-aflibercept, or a biosimilar of aflibercept/ziv-aflibercept systemically at any time
29. Any IVT therapy, including adrenocorticotropic hormone, in the study or fellow eye, or intramuscular or intravenous corticosteroids within 4 weeks before randomization. The use of long-acting steroids, either systemically or intraocularly, in the 3 months before randomization

30. Currently receiving treatment with another investigational device or study drug, or less than 30 days or 5 half-lives (whichever is longer) since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded

General

31. For women: pregnant or breast feeding, or planning to become pregnant while enrolled in the study and for 3 months after the last dose of investigational product
32. Sexually active subjects and their partners who are of childbearing potential (ie, neither surgically sterile nor postmenopausal) and not agreeing to use adequate contraception (eg, true abstinence, sterilization, birth control pills, Depo Provera injections, contraceptive implants, or other effective methods) while on study and for 3 months after the last dose of study drug. Male subjects must agree not to donate sperm during study and for 3 months following treatment with test article or until the scheduled end of the study (whichever is longer)
33. Allergy or hypersensitivity to investigational product, to any of the excipients of ABP 938 or aflibercept, or to other study-related procedures/medications (eg, anesthesia, antiseptic, fluorescein dye)
34. History or evidence of any other clinically significant disorder, condition, or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion
35. Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, Clinical Outcome Assessments) to the best of the subject and investigator's knowledge

Test product:

Name: ABP 938

Dose: 2 mg (0.05 mL) every 4 weeks for the first 3 doses, followed by 2 mg (0.05 mL) once every 8 weeks.

Mode of administration: IVT injection

Reference Product:

Name: aflibercept

Dose: 2 mg (0.05 mL) every 4 weeks for the first 3 doses, followed by 2 mg (0.05 mL) once every 8 weeks.

Mode of administration: IVT injection

Statistical methods: The primary analysis of primary and secondary efficacy endpoints will be based on the Full Analysis Set (FAS), consisting of all randomized subjects, based on the treatment the subject is randomized to.

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.

Clinical equivalence will be evaluated by comparing the 95% confidence interval (CI) of the treatment difference between ABP 938 and aflibercept in the primary endpoint, change from baseline in BCVA at week 8, with an equivalence margin of (-3.9, 3.9) letters. The least squares (LS) mean difference between the 2 treatment groups and the corresponding 95% CI will be estimated using an analysis of covariance (ANCOVA) model for the week 8 BCVA change from baseline adjusted for region and baseline BCVA. Consistency in treatment effects between the East Asian subjects and the overall population will be evaluated by descriptive summaries and/or graphical displays.

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. Sensitivity analyses will be conducted to evaluate the robustness of the result to potential departure from the MCAR assumption.

Secondary efficacy endpoints will be analyzed descriptively. BCVA, CNV, and CST changes from baseline will be summarized by visit. The LS mean differences and 95% CIs will be estimated using ANCOVA models similar to that used for the primary endpoint. Generalized linear models with identity link will be utilized to obtain the point estimate and 95% CIs for treatment differences in proportions of subjects gaining ≥ 10 letters at week 8, maintaining vision at week 52, and gaining ≥ 15 letters at week 52.

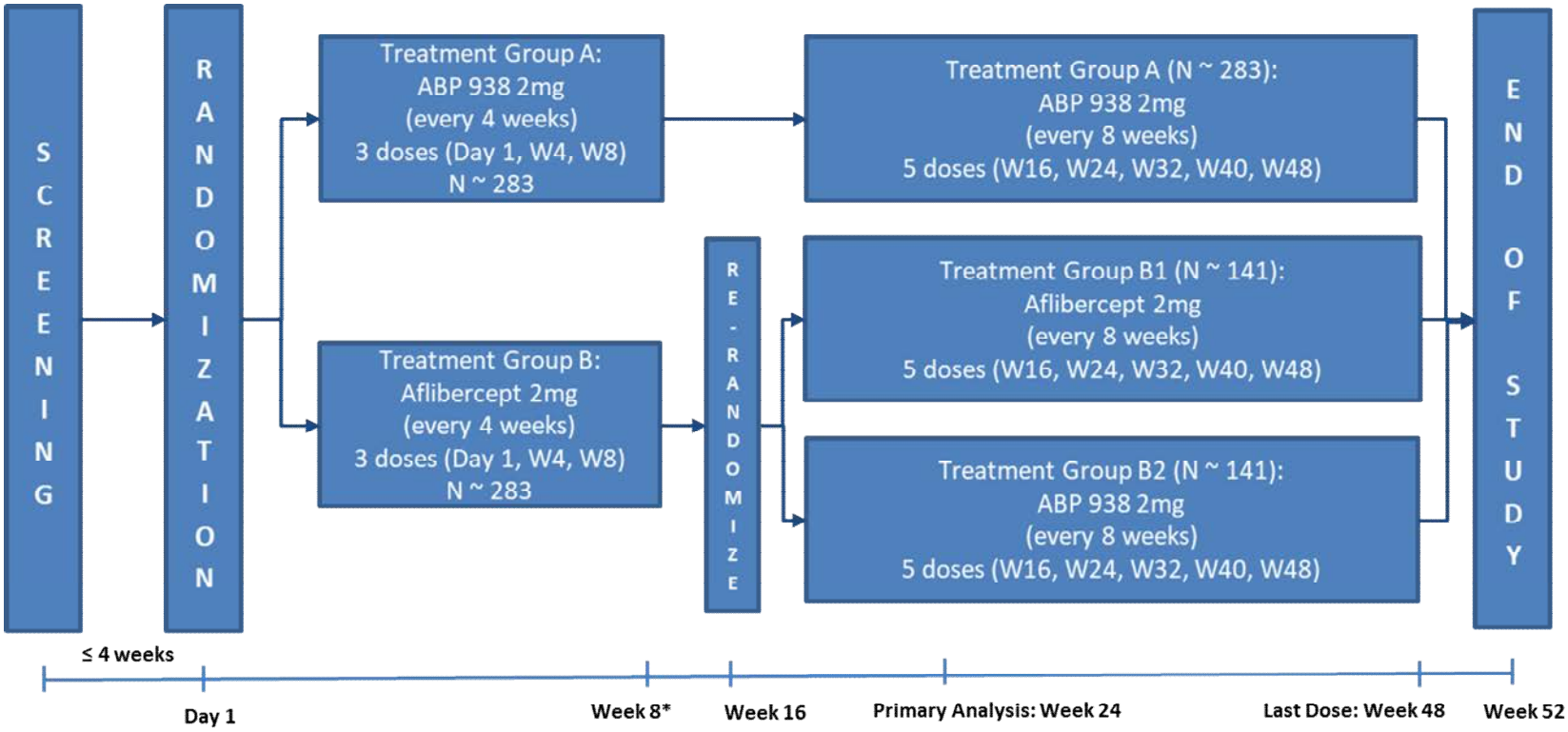
Sensitivity analyses will be performed on the primary and key secondary efficacy endpoints in the Per Protocol Analysis Set. The Per Protocol Analysis Set is a subset of FAS, which includes subjects who have completed dosing at day 1 and week 4 and have completed BCVA assessment at week 8 without experiencing a protocol deviation that may affect their evaluation for the primary endpoint of the study.

Safety will be assessed descriptively in the Safety Analysis Set, including all treated subjects who received at least 1 dose of investigational product. Subject level safety data and safety data for the study eye will be summarized descriptively and separately for day 1 through week 8, day 1 through week 16, week 16 through the EOS visit, and day 1 through the EOS visit, based on actual treatment received in the study eye. The summaries for day 1 through week 8 and day 1 through week 16 will be presented by treatment (ABP 938 vs. aflibercept). The summaries for week 16 through the EOS visit and day 1 through the EOS visit will be presented by treatment sequence (ABP 938/ABP 938 vs. aflibercept/aflibercept vs. aflibercept/ABP 938) for subjects who are re-randomized and treated post re-randomization. For the subset of subjects who also have the fellow eye treated with the investigational product, their safety data collected for the fellow eye from the first investigational product treatment of the fellow eye to the EOS visit will be summarized similarly, and summaries will be based on the actual treatment received in the fellow eye. All reported adverse events will be assigned the system organ class and preferred term according to the Medical Dictionary for Regulatory Activities dictionary as of the time of analysis and graded by Common Terminology Criteria for Adverse Events version 4.03. The number and percent of subjects reporting treatment-emergent adverse events (all, serious, and fatal) and EOIs will be tabulated. Laboratory data, vital signs, and ophthalmoscopic assessments will be summarized by visit. The number and percent of subjects developing ADAs will be tabulated by visit.

Pharmacokinetic concentration data from the PK substudy will be summarized descriptively by visit for the PK Analysis Set, consisting of subjects in the PK substudy who receive at least 1 dose of investigational product between day 1 and week 8 (inclusive) and who have at least 1 reported serum concentration of ABP 938 or aflibercept.

Statistical hypothesis: ABP 938 is equivalent to aflibercept in the treatment of neovascular (wet) AMD.
Protocol version and date: Version 4.0, **16 May 2022**

Figure 1 Study Schematic



*Primary Endpoint assessment will be performed at Week 8.

Table 1 Schedule of Activities

	Screening	Baseline	Week (± 3 days)		Week (± 5 days)					End of Study[l] (± 5 days)
		day 1 (week 0)	4	8	16[l]	24	32	40	48	52
Clinical Assessments										
Informed Consent	X									
Medical/treatment history	X									
Physical examination	X			X						X
Height and weight	X									
Vital signs	X	X		X	X					X
ECG	X									
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse events	X[a]	X	X	X	X	X	X	X	X	X
Treatment										
Randomization		X			X					
ABP 938/aflibercept[b]		X	X	X	X	X	X	X	X	
Disease Assessment										
Indirect ophthalmoscopy[c,d]	X	X	X	X	X	X	X	X	X	X
Slit-lamp[d,e]	X	X	X	X	X	X	X	X	X	X
IOP[d,f]	X	X	X	X	X	X	X	X	X	X
BCVA using ETDRS chart	X	X	X	X	X	X	X	X	X	X
Fluorescein angiography (FA)	X			X	X	X				X
Fundus Photography (FP)	X			X	X	X				X
Spectral domain optical coherence tomography (SD-OCT)	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments										
Serum chemistry	X	X		X	X					X
Hematology	X	X		X	X					X
PT, aPTT, and INR	X									
PK samples (substudy subjects only)[g]		X[h]		X[i]						
Anti-drug antibodies[j]		X		X	X	X		X		X
Urinalysis	X	X		X	X					X
Pregnancy[k]	X	X								

ADA = antidrug antibody; BCVA = best corrected visual acuity; ECG = electrocardiogram; ETDRS = Early Treatment Diabetic Retinopathy Study; INR = international normalized ratio; IOP = intraocular pressure; PK = pharmacokinetics; PT = prothrombin time; aPTT = activated partial thromboplastin time

a Only serious adverse events are reported during the screening period.

b ABP 938/aflibercept will be administered after all other procedures are completed for each visit (except for postdose **slit-lamp examination** and postdose IOP), ensuring that the study eye is administered first, then the fellow eye. If the subject presents with an infection at the dosing visit(s), the administration of investigational product may be delayed (up to 3 days for weeks 4 and 8, and up to 5 days for doses thereafter). In the case of delayed or missed dose for any reason, subsequent doses should be administered according to the original schedule (ie, at the planned timepoint relative to first dose).

c Examination of the retina of the study eye to be performed with pupil dilation. Predose on treatment days.

d Procedure will be **performed for** the fellow eye on the day of investigational product administration to the fellow eye**,** including the EOS visit (if the fellow eye is dosed).

e Predose (on the day of injection) and postdose (within 60 minutes) slit-lamp examination to be performed with pupil dilation on treatment days. Single, postdilation examination on other days.

f IOP should be measured predose (on the day of injection) and postinjection (at minimum 15 minutes and no longer than 60 minutes) on treatment days. Single examination on other days.

g For subjects who have consented for the PK substudy only: approximately 32 subjects who have consented for the PK sub study will have PK samples collected at the timepoints noted. If it is anticipated that the fellow eye will need to be treated prior to the week 8postdose PK sample, then the subject should not be enrolled into the PK substudy. If an enrolled PK substudy subject develops **a need** for **treatment of the** fellow eye prior to **the** 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.

h This measurement will be taken predose (within 60 minutes before day 1 dose) and postdose (approximately 24 hours after the day 1 dose), with an allowable window of: -6 hours to +24 hours (ie, 18 hours to 48 hours after day 1 dose).

i PK sample collection window 1 day after week 8 dose: -6 hours to +24 hours (ie, 18 hours to 48 hours after week 8 dose). Details will be provided in an Investigator Laboratory Manual.

j ADA samples should be taken within 3 hours prior to administration of investigational product into either eye at the study visits noted in schedule above. Details will be provided in an Investigator Laboratory Manual.

k Required for females of childbearing potential. Serum pregnancy test will be done at screening by the central laboratory. A urine pregnancy test will be performed locally. Additional local urine pregnancy tests should be done as per local requirements as needed.

l Subjects who are unable to complete the week 16 visit within the visit window will not be re-randomized and will be discontinued from the study. For subjects who discontinue from the study or terminate study early, perform all the end-of-study procedures scheduled for week 52 within 28 days from determining that the subject will discontinue from the study.

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LIST OF ABBREVIATIONS

ADA	antidrug antibody
ADR	adverse drug reactions
AMD	age-related macular degeneration
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
BCVA	best corrected visual acuity
CFR	Code of Federal Regulations
CI	confidence interval
CNV	choroidal neovascularization
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRT	central retinal thickness
CSR	clinical study report
CST	central subfield thickness
CTCAE	Common Terminology Criteria for Adverse Events
DMC	data monitoring committee
DME	diabetic macular edema
DR	diabetic retinopathy
ECG	electrocardiogram
EDC	electronic data capture
EOI	event of interest
EOS	end-of-study
ETDRS	Early Treatment Diabetic Retinopathy Study
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FA	fluorescein angiography
FAS	Full Analysis Set
Fc	fragment crystallizable
FDA	Food and Drug Administration
FP	Fundus Photography
FSH	follicle-stimulating hormone
GCP	Good Clinical Practices

HIPAA	Health Insurance Portability and Accountability Act
HRT	hormonal replacement therapy
IB	investigator's brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	independent ethics committee
IOP	intraocular pressure
IRB	institutional review board
IVT	intravitreal
IXRS	Interactive Web/Voice Response System
LS	least squares
MCAR	**missing completely at random**
OCT	optical coherence tomography
PK	pharmacokinetic(s)
PlGF	placental growth factor
PT	prothrombin time
QTL	quality tolerance limit
RVO	retinal vein occlusion
SAP	Statistical Analysis Plan
SD-OCT	spectral domain optical coherence tomography
TMF	trial master file
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell
YAG	yttrium aluminum garnet

1 Introduction and Rationale

1.1 Background

Age-related macular degeneration (AMD) is the leading cause of irreversible central vision loss and blindness in individuals older than 50 years in developed countries (1). It is generally painless and leads to the gradual impairment of vision, but it can sometimes cause a rapid reduction in vision. The prevalence of AMD is higher among white individuals and increases with age. Prevalence is approximately 1% among white individuals in their 50s and increases to 15% among those in their 80s (2).

AMD is a disease spectrum with early and later stages and can be divided into 2 categories. The non-neovascular ('dry') AMD is the most common form and accounts for about 80% of AMD cases. The most severe vision loss occurs in the neovascular (or wet) form of AMD, and it is responsible for nearly 90% of the severe central visual acuity loss from neovascular (wet) AMD (2). Early treatments, such as laser ablation (3) and photodynamic therapy with verteporfin (4), slowed severe vision loss but rarely resulted in stabilization or improvement. Neovascular (wet) AMD appears to be driven by choroidal neovascularization (CNV), which results in retinal swelling and edema (5), and the vesicular abnormality is regulated by vascular endothelial growth factor (VEGF). Inhibition of VEGF can lead to visual improvement, and intravitreal (IVT) anti-VEGF therapy is the current gold standard for treatment. The current primary treatments for neovascular (wet) AMD are a humanized, monoclonal, anti-VEGF antibody antigen **binding** fragment (FAB), ranibizumab (Lucentis®) and a recombinant, high-affinity human VEGF receptor (VEGFR), aflibercept (Eylea®).

1.1.1 Amgen Investigational Product ABP 938 Background

Amgen is developing ABP 938 as a biosimilar candidate to Eylea® (aflibercept). In the US, aflibercept is approved for IVT administration in the treatment of neovascular (wet) AMD, macular edema following retinal vein occlusion (RVO), diabetic macular edema (DME), and diabetic retinopathy (DR) in patients with DME (6). In the EU, aflibercept is approved for the treatment of the above indications with the exception of DR, and is also approved for the treatment of myopic CNV (7).

ABP 938 has the same amino acid sequence, dosage form, route of administration, and product strength as aflibercept, but it will have a different formulation containing compendial excipients at final drug product concentrations approved for IVT administration.

ABP 938 and aflibercept belong to the pharmacologic class of VEGF inhibitors. Like aflibercept, ABP 938 is a recombinant fusion protein consisting of portions of human VEGFRs 1 and 2 extracellular domains fused to the fragment crystallizable (Fc) portion of human immunoglobulin isotype class G subclass 1 monoclonal antibody. ABP 938 and aflibercept are produced by recombinant DNA technology in mammalian Chinese hamster ovary cell expression systems and purified by processes that include specific viral inactivation and filtration steps. The mechanism of action across indications involves the protein molecule acting as a soluble decoy receptor that binds VEGF type A (VEGF-A) and placental growth factor (PlGF), and to a lesser extent VEGF type B (VEGF-B), with higher affinity than their native receptors, and thereby inhibits binding and activation of VEGFR-1 and VEGFR-2.

The totality of evidence available to date from an ongoing analytical program suggests that ABP 938 is analytically similar to aflibercept with respect to identity, general properties, primary and higher order structure, carbohydrate structure, purity and impurity profile, and biological activity.

A detailed description of the chemical and nonclinical data of ABP 938 is provided in the Investigator's Brochure (IB).

ABP 938 has not been tested in humans to date. Based on the demonstration of analytical and nonclinical similarity of ABP 938 and aflibercept, the clinical efficacy and safety information for aflibercept as described in the product labeling for Eylea® (Eylea® USPI [6], Eylea® SmPC [7]) are considered relevant to predicting the effects of ABP 938 in humans (Section 1.1.2).

1.1.2 Non-Amgen Investigational Product Aflibercept

As described above for ABP 938, aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF, and to a lesser extent VEGF-B, with higher affinity than their native receptors, and thereby inhibits binding and activation of VEGFR-1 and VEGFR-2 (6).

Systemic drug exposure following IVT administration of aflibercept is negligible. In patients with neovascular (wet) AMD, following IVT administration of aflibercept at 2 mg per eye, the free aflibercept plasma concentrations were undetectable 2 weeks post-dosing in all patients. After a 2 mg aflibercept IVT administration to patients, the mean peak concentration of free aflibercept is more than 100-fold lower than the concentration of aflibercept required to half maximally bind systemic VEGF. Consistent with this, no systemic effects (eg, changes in blood pressure) were observed after IVT aflibercept administration to patients (6,8,9).

When aflibercept was administered to subjects with neovascular (wet) AMD in clinical studies, anatomic measures of disease activity improved similarly in all treatment groups from baseline to week 52; when administered to subjects with RVO and DME, reductions in mean retinal thickness were observed at week 24 compared to baseline and at weeks 52 and 100 compared to baseline, respectively (6).

Adverse events reflected in the warnings and precautions section of the product labeling for aflibercept that may be serious include endophthalmitis and retinal detachment, increase in intraocular pressure (IOP), potential for immunogenicity, arterial thromboembolic events (including nonfatal stroke, nonfatal myocardial infarction, or vascular death [including deaths of unknown cause]), traumatic cataract, cataract, vitreous haemorrhage, vitreous detachment, intraocular inflammation, hypersensitivity, conjunctival hemorrhage, visual acuity reduced, eye pain, and vitreous floaters (6,7).

1.2 Study Rationale

In the US, EU, and much of the world, laws, regulations, and guidance have been put in place to increase availability of biological treatments by developing and licensing biosimilar products (10,11,12,13,14). A biosimilar product, generally, is highly similar to a licensed biologic reference product, and there are no clinically meaningful differences between the biosimilar and reference products in terms of safety, purity, and potency. Biosimilarity is demonstrated by the totality of the evidence, including analytical, nonclinical, and clinical evidence. The analytical similarity of ABP 938 and aflibercept is summarized in more detail in the IB.

Given the biochemical and nonclinical similarity of ABP 938 to aflibercept, a human study to fully establish biosimilarity is warranted. Because pharmacokinetic (PK) exposure following IVT administration is negligible and not informative as a demonstration of similarity, a PK similarity study will not be performed, but a PK substudy of the current study will be performed to assess the similar minimal systemic exposure of ABP 938 and aflibercept, and thereby support a demonstration of no clinically meaningful differences between ABP 938 and aflibercept.

The current study is designed to demonstrate the clinical similarity between ABP 938 and aflibercept in terms of efficacy, safety, and immunogenicity for subjects with neovascular (wet) AMD (10,11,12,13,14). In addition, subjects will be recruited in East Asia to assess consistency of results between the East Asian subgroup and the overall study population.

1.3 Benefit/Risk Assessment

ABP 938 is expected to be biosimilar to aflibercept. The risks and benefits of ABP 938 are therefore expected to be the same as those of aflibercept, as specified in the product labeling and summarized in Section 1.1.2. All subjects in this study will receive an active treatment.

More detailed information about the expected benefits, risks, and reasonably expected adverse events of ABP 938 can be found in the IB.

Considering the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with ABP 938 are justified by the anticipated benefits that may be afforded to subjects with neovascular (wet) AMD.

A risk assessment will be performed on an ongoing basis to evaluate the potential impact of coronavirus disease 2019 (COVID-19) on subjects. Risk mitigation measures, including COVID-19 related precautions and procedures (including severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] testing/screening) will be implemented based on the prevailing situation during study conduct, at the investigator's discretion and in accordance with local and institutional guidelines, as applicable.

2 Study Objectives, Endpoints, and Estimand

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 CNV area 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) 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.

3 Study Plan

3.1 Overall Study Design and Plan

This is a randomized, double-masked, active controlled multiregional clinical study in adult subjects with neovascular (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 IVT injection every 4 weeks for the first 3 doses (ie, 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 EOS 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 terminate early. An external, independent data monitoring committee (DMC) will evaluate the safety data throughout the study.

For subjects receiving neovascular (wet) AMD treatment in the fellow eye during the study, sites must request an additional box of investigational product. Refer to Section 6.5.

Approximately 32 subjects will be consented and enrolled into a PK substudy. These subjects will have a PK sample collected predose (within 60 minutes before day 1 dose) and postdose (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.

3.2 Discussion of Study Design

This study is randomized and double-masked to prevent bias in treatment allocation and in the subjective assessment of effect. The re-randomization at week 16 will allow a masked evaluation of the effects of a single transition from aflibercept to ABP 938.

All subjects will receive active treatment in accordance with the approved aflibercept product labeling. The population is selected to be sensitive enough to detect any clinical differences between ABP 938 and aflibercept. The efficacy measures were selected to make a meaningful comparison of the effects and are similar to those in the aflibercept product labeling. The safety measures are standard and well understood and include ophthalmologic assessments and the assessment of ADAs, as this is protein product.

3.3 End of Study

3.3.1 End-of-Study Definition

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

In this study, the primary endpoint is assessed at week 8, and subjects will remain on treatment for up to 48 weeks for assessment of safety and secondary endpoints. The primary completion date will be the date when the last subject is assessed for week 8 visit or terminates early. The primary analysis will be performed when all subjects reach week 24 or terminate early. The final analysis will be performed when all subjects complete the week 52 visit or terminate early.

End of Study: The EOS date is defined as the date when the last subject across all centers is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

3.3.2 Study Duration for Subjects

The study consists of a screening period of up to 4 weeks, a treatment period of 48 weeks, followed by a safety follow-up period through week 52, for a total study duration of up to 56 weeks.

4 Study Population

Both eyes will be assessed at the screening visit for eligibility, and only 1 eye will be selected from each subject as the study eye. In case both eyes meet the eligibility criteria, the study eye will be the one with the worst BCVA. All images will be sent to central imaging vendor for confirming eligibility.

4.1 Inclusion Criteria

The following inclusion criteria must be met for a subject to be eligible for inclusion in the study:

1. Subjects or their legally authorized representative must sign an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form (ICF) before any study-specific procedures
2. Men or women ≥ 50 years old
3. Subjects must be diagnosed with neovascular (wet) AMD in the study eye (confirmed by central imaging vendor before randomization)
4. Active, treatment naïve subfoveal CNV lesions secondary to neovascular (wet) AMD including juxtafoveal lesions that affect the fovea as confirmed with SD-OCT, FA and**/or** FP in the study eye (confirmed by central imaging vendor before randomization)
5. BCVA between 73 and 34 letters, inclusive, in the study eye using ETDRS testing
6. Presence of intra and/or subretinal fluid as identified by SD-OCT attributable to active CNV in the study eye (confirmed by central imaging vendor before randomization)
7. Central retinal thickness (CRT) of > 270 µm in the study eye as measured by the machine, calculated average thickness in the ETDRS central 1 mm subfield (CST) by SD-OCT at screening (confirmed by central imaging vendor before randomization)

4.2 Exclusion Criteria

A subject who meets any of the following exclusion criteria will not be eligible for inclusion in the study:

EYE RELATED

Subjects are excluded if they meet any of the following criteria in the study eye:

1. Total lesion size > 12 disc areas (30.5 mm^2, including blood, scars, and neovascularization) in the study eye (confirmed by central imaging vendor before randomization)
2. Active CNV area (classic plus occult components) that is < 50% of the total lesion area in the study eye (confirmed by central imaging vendor before randomization)
3. Scar, fibrosis, or atrophy involving the center of the fovea in the study eye (confirmed by central imaging vendor before randomization)

4. Presence of retinal pigment epithelium tears or rips involving the macula in the study eye (confirmed by central imaging vendor before randomization)
5. History of any vitreous hemorrhage within 4 weeks before randomization in the study eye
6. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of 8 diopters or more negative or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye (confirmed by central imaging vendor before randomization with the exception of the refractive error and axial length which is to be assessed by the investigator)
7. Prior vitrectomy or laser surgery of the macula (including photodynamic therapy or focal laser photocoagulation) in the study eye
8. History of retinal detachment in the study eye
9. Any history of macular hole of stage 2 and above in the study eye
10. Any macular pathology that might limit vision i.e., Vitreomacular traction or significant epiretinal membrane (confirmed by central imaging vendor before randomization) in the study eye
11. Any intraocular or periocular surgery within 3 months before randomization on the study eye, except lid surgery, which may not have taken place within 4 weeks before randomization, as long as it is unlikely to interfere with the injection
12. Prior trabeculectomy or other filtration surgery in the study eye
13. Uncontrolled glaucoma (defined as intraocular pressure [IOP] ≥ 25 mmHg despite treatment with antiglaucoma medication) in the study eye
14. Aphakia or pseudophakia with complete absence of posterior capsule (unless it occurred as a result of a yttrium aluminum garnet [YAG] posterior capsulotomy) in the study eye
15. Previous therapeutic radiation in the region of the study eye
16. History of corneal transplant or corneal dystrophy in the study eye

17. Significant media opacities, including cataract, which might interfere with visual acuity or assessment of safety, in the study eye

18. Any concurrent intraocular condition other than neovascular (wet) AMD in the study eye that, in the opinion of the investigator, requires planned medical or surgical intervention during the study or increases the risk to the subject beyond what is expected from standard procedures of intraocular injection, or which otherwise may interfere with the injection procedure or with evaluation of efficacy or safety

Subjects are excluded if they meet any of the following criteria in either eye:

19. History or clinical evidence of uveitis, diabetic retinopathy, diabetic macular edema, or any other vascular disease affecting the retina, other than neovascular (wet) AMD (confirmed by central imaging vendor before randomization)

20. Active intraocular inflammation or active or suspected ocular or periocular infection, within 2 weeks before randomization

21. Active scleritis or episcleritis or presence of scleromalacia

Other Medical Conditions

22. Active extraocular infection or history of extraocular infections as follows:

    a. any active infection for which systemic anti-infectives were used within 4 weeks before randomization

    b. recurrent or chronic infections or other active infection that, in the opinion of the investigator, might cause this study to be detrimental to the subject

23. Acute coronary event or stroke within 3 months before randomization

24. Uncontrolled, clinically significant systemic disease such as diabetes mellitus, hypertension, cardiovascular disease including moderate to severe heart failure (New York Heart Association class III/IV), renal disease, or liver disease

25. Malignancy within 5 years EXCEPT treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, OR in situ breast ductal carcinoma

Washouts and Nonpermitted Treatments

26. Any prior ocular or systemic treatment, including another investigational product or surgery for neovascular (wet) AMD (including anti-vascular endothelial growth factor [VEGF] therapy) in the study eye, except dietary supplements or vitamins
27. Any ocular or systemic treatment including another investigational product or surgery for neovascular (wet) AMD (including anti-VEGF therapy) in the fellow eye, within 30 days before randomization, except dietary supplements or vitamins
28. Prior systemic anti-VEGF treatment as follows:
    a. Investigational or approved anti-VEGF therapy systemically within 3 months before randomization
    b. Aflibercept, ziv-aflibercept, or a biosimilar of aflibercept/ziv-aflibercept systemically at any time
29. Any IVT therapy, including adrenocorticotropic hormone, in the study or fellow eye, or intramuscular or intravenous corticosteroids within 4 weeks before randomization. The use of long-acting steroids, either systemically or intraocularly, in the 3 months before randomization
30. Currently receiving treatment with another investigational device or study drug, or less than 30 days or 5 half-lives (whichever is longer) since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded

General

31. For women: pregnant or breast feeding, or planning to become pregnant while enrolled in the study and for 3 months after the last dose of investigational product
32. Sexually active subjects and their partners who are of childbearing potential (ie, neither surgically sterile nor postmenopausal) and not agreeing to use adequate contraception (eg, true abstinence, sterilization, birth control pills, Depo Provera injections, contraceptive implants, or other effective methods) while on study and for 3 months after the last dose of study drug. Male subjects must agree not to donate sperm during study

and for 3 months following treatment with test article or until the scheduled end of the study (whichever is longer)

33. Allergy or hypersensitivity to investigational product, to any of the excipients of ABP 938 or aflibercept, or to other study-related procedures/medications (eg, anesthesia, antiseptic, fluorescein dye)
34. History or evidence of any other clinically significant disorder, condition, or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion
35. Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, Clinical Outcome Assessments) to the best of the subject and investigator's knowledge

4.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written IRB/IEC approval of the protocol, ICF, and all other subject information and/or recruitment material.

The subject or his/her legally authorized representative must personally sign and date the IRB/IEC and Amgen approved ICF before commencement of study specific procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria and has been randomized in the Interactive Web/Voice Response System (IXRS). The investigator is to document this eligibility decision and date in the subject's medical record.

Each subject will have a unique subject identification number obtained from the IXRS. This will be assigned at the screening visit. The unique 11-digit subject identification will be assigned in sequential order for each site in the format "542XXXXX###," where "542XXXXX" refers to the site number and "###" refers to the sequential subject ordering as each subject at a site is entered into the IXRS (eg, 54212345001). This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The investigator will keep a record (the subject

screening log) that includes limited information (such as date of screening) about the potential candidates for subjects who entered screening.

If a subject withdraws from study participation, his/her unique identification number(s) cannot be re-used for another subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. This number will not necessarily be the same as the randomization number assigned for the study.

4.4 Screen Failures

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Laboratory assessments used to determine subject eligibility may be repeated during the screening period before the subject is considered a screen failure. Screen failed subjects may be rescreened up to 2 times at the investigator's discretion (ie, a total of 3 screens including initial screening). If screening procedures cannot be completed within 28 days before day 1, the subject will be considered a screen failure but may be eligible for rescreening. The subject will retain the same subject identification number provided at initial screening. These subjects can be rescreened under the same ICF if rescreening and randomization occurs within 30 days of initial consent date. If it is longer than 30 days from the initial consent, the subject will need to be re-consented.

4.5 Premature Discontinuation

Subjects have the right to withdraw from investigational product, protocol procedures, or the study completely at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

4.5.1 Premature Discontinuation of Investigational Product

Subjects (or a legally authorized representative) can decline to continue receiving investigational product or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product and must discuss with the subject

the possibilities for continuation of the Schedule of Activities (see Table 1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is recommended that these subjects remain on study to ensure safety surveillance and/or collection of efficacy data, where possible.

Reasons for early removal from protocol-required investigational product(s) or procedural assessments may include any of the following:

- Decision by sponsor
- Lost to follow-up
- Death
- Adverse event
- Subject request
- Protocol deviation
- Noncompliance
- Pregnancy

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 EOS visit within 28 days from determining that the subject will discontinue from the study.

4.5.2 Premature Discontinuation from the Study

Participation in the study is strictly voluntary. A subject (or a legally authorized representative) has the right to withdraw from the study at any time for any reason, without any reprisal.

The investigator has the right to terminate participation of a subject for any of the following reasons:

- Violation of the protocol

- Requirement for alternative therapy or alternative dosing schedule (eg, subjects who require treatment every 4 weeks) per the investigator's determination
- Severe adverse events or serious adverse events
- Any other reason relating to the subject's safety or integrity of the study data
- Noncompliance with study procedures

If a subject is withdrawn from the study, the Clinical Research Associate will be informed immediately. Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study, and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the study center study records and notify the sponsor or designee.

Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a study, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

At the time of premature study discontinuation, the investigator should make every effort to ensure the subject completes the assessments indicated at the EOS visit within 28 days from determining that the subject will discontinue from the study; see Table 1.

Subjects who prematurely discontinue from the study cannot subsequently rejoin the study.

For details on the discontinuation of study centers or the study as a whole, see Section 14.

4.5.3 Lost to Follow-up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The study center must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator (or designee) must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject notes.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

5 Description of Study Assessments

A full Schedule of Activities is presented in Table 1.

5.1 Demographics and Other Screening Assessments

Safety assessments that are also part of the screening assessments are described in Section 5.3.

5.1.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the IRB/IEC approved ICF before any study-specific procedures are performed.

5.1.2 Medical History

Medical history, including any ongoing illnesses, will be recorded in the case report form (CRF), with the start date and stop date (if applicable) of the illness/condition.

5.1.3 Demographics

Demographic data, including (where permitted), date of birth/age, sex, race, and ethnicity will be collected.

5.1.4 Disease-Specific Medical History

Neovascular (wet) AMD history will be collected.

5.2 Efficacy Assessments

5.2.1 Best Corrected Visual Acuity

The BCVA will be recorded using ETDRS charts at screening and each visit (for the study eye) thereafter as described in the Study Manual. Whenever possible, postbaseline assessments will be performed by the same assessor that performed the baseline assessment.

5.2.2 Fluorescein Angiography

Fluorescein angiography will be taken using a standardized protocol approved by the central reading center at the visits specified in the Schedule of Activities (Table 1).

Study sites and imaging personnel will be certified by the central reading center for fluorescein angiography. All imaging assessments should be done on central reading center certified equipment and by a central reading center certified technician. All post baseline assessments should be done on the same equipment that was used for the baseline assessment.

All images will be sent to central imaging vendor. See imaging manual for more information.

5.2.3 Spectral Domain Optical Coherence Tomography

SD-OCT parameters will be obtained of the posterior pole per standard protocols approved by the central reading center. The CST is defined as the average thickness in the ETDRS central 1 mm diameter subfield (the central subfield).

Study sites and imaging personnel will be certified by the central reading center for SD-OCT scans. All imaging assessments should be done on central reading center certified equipment and by a central reading center certified technician. All post baseline assessments should be done on the same equipment that was used for the baseline assessment.

All images will be sent to central imaging vendor. See imaging manual for more information.

5.2.4 Fundus photography

Fundus photography evaluates vascular and structural changes in the eye by capturing images of posterior pole of eye (fundus). The central and peripheral retina, optic disc and macula will be examined. Fundus photography will be taken using a standardized protocol approved by the central reading center at the visits specified in the Schedule of Activities (Table 1).

Study sites and imaging personnel will be certified by the central reading center for fundus photography. All imaging assessments should be done on central reading center certified equipment and by a central reading center certified technician. All post baseline assessments should be done on the same equipment that was used for the baseline assessment.

All images will be sent to central imaging vendor. See imaging manual for more information.

5.3 Safety Assessments

5.3.1 Adverse Events

Adverse events are defined in Section 7.1.1. Adverse events will be followed, recorded, and reported in line with the procedures described in Section 7.3.

5.3.2 Clinical Laboratory Evaluations

With the exception of urine pregnancy test, all laboratory assessments will be performed by a central laboratory. Blood and urine samples will be collected at the times indicated in Table 1. At visits when investigational product is administered, clinical laboratory samples will be collected before investigational product administration.

The following parameters will be assessed:

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, amylase, aspartate aminotransferase, calcium, creatinine, gamma glutamyltransferase, glucose, lipase, potassium, sodium, and total bilirubin

Coagulation: international normalized ratio, prothrombin time (PT), activated partial thromboplastin time (aPTT)

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

A serum pregnancy test will be performed at screening by the central laboratory. A urine pregnancy test will be performed locally. Additional local urine pregnancy tests should be done as per local requirements as needed.

Refer to the Investigator Laboratory Manual for details regarding the collection, processing, and shipping of the blood and urine samples.

The investigator must review the laboratory report as described in Section 7.1.3.

Any blood samples (eg, PK, immunogenicity) collected according to the Schedule of Activities (Table 1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

5.3.3 Slit-Lamp Examination

Slit-lamp biomicroscopy will be used to examine eye structures for both eyes during screening and the study eye at each study visit. At screening, slit-lamp examinations will be performed according to local standard of care. On days of investigational product administration, slit-lamp examinations will be done before investigational product is administered and again within 60 minutes after investigational product administration; both examinations will be performed postdilation. If a subject receives investigational product in the fellow eye, that eye will also be examined at all study visits, including end of study. Slit-lamp examinations will include lids, conjunctiva, cornea, anterior chamber, iris, pupil, lens, and anterior vitreous, and will be performed according to local standards.

5.3.4 Indirect Ophthalmoscopy

Indirect ophthalmoscopy will be used to examine the retina of both eyes during screening and the study eye at each subsequent study visit, and will be performed with pupil dilation.

At visits when investigational product is administered, indirect ophthalmoscopy will be performed before investigational product administration. If a subject receives investigational product in the fellow eye, that eye will also be examined at all study visits, including end of study. Indirect ophthalmology will include retina vessels, macula, fovea, periphery, optic nerve, and vitreous, and will be performed according to local standards.

5.3.5 Intraocular Pressure

IOP will be measured for both eyes during screening and the study eye at each study visit. IOP will be measured according to the standard procedure at each site. At visits when investigational product is administered, IOP will be measured before investigational product is administered and again at minimum 15 minutes and no longer than 60 minutes after investigational product administration. If a subject receives investigational product in the fellow eye, that eye will also be examined at all study visits, including end of study.

The examiner will measure IOP and record results in mmHg with 1 decimal place (eg, 24.0). The method of IOP measurement used must remain consistent throughout the study and must be calibrated for accuracy according to manufacturer's instructions throughout the study.

5.3.6 Pregnancy

Details of all pregnancies and/or lactation in female subjects and female partners of male subjects that occur after the start of study treatment and until 3 months after the last IVT injection will be collected.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Section 17.2. Amgen or its designee will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Section 17.2.

5.3.7 12-lead Electrocardiogram

Electrocardiograms (ECGs) will be read locally at screening. Computerized 12-lead ECG recordings will be obtained after the subject has been supine for 5 minutes. Each lead will be recorded for at least 3 to 5 beats at a speed of 25 mm/sec paper speed and 10 mm/mV amplitude. At a minimum, heart rate, P-wave, PR-interval, QRS-wave, QT-interval, and corrected QT-intervals (msec) will be recorded from the 12-lead ECG. A copy of the ECGs will be retained at the study center. For the purposes of screening, the investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically acceptable for inclusion, if abnormal.

5.3.8 Vital Signs

Vital signs will be measured in a semi-supine or sitting position after 5 minutes' rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiratory rate. Vital signs should be assessed in the same position (either semi-supine or sitting position) throughout the study.

5.3.9 Physical Examination

Subjects will undergo complete and brief physical examinations, as indicated in the Schedule of Activities (Table 1). Physical examination findings will be recorded.

Physical examinations will be performed by a physician and will include examination of the following: general appearance, head, ears, eyes, nose, throat, neck, skin, cardiovascular system, respiratory system, abdominal system, and nervous system. For each body system, an assessment of normal or abnormal will be recorded. Clinically relevant changes from baseline will be reported as adverse events.

Body weight and height will be measured and recorded as indicated in Table 1. The subject should be dressed in light clothing, without shoes or jacket.

Investigators should pay special attention to clinical signs related to previous serious illnesses. Any new abnormalities or worsening of existing abnormalities should be reported as adverse events, as appropriate (see Section 7).

5.4 Pharmacokinetics

PK will be assessed only in a subset of approximately 32 subjects who consent to participate in the PK substudy. PK samples will be collected predose (within 60 minutes before day 1 dose) and postdose (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. Instructions for the collection and handling of biological samples will be provided in the Investigator Laboratory Manual. The actual date and time of collection of each sample will be recorded.

5.5 Antidrug Antibodies

Blood samples for ADA assessments will be collected at the time points indicated in Table 1. ADA samples should be taken within 3 hours prior to administration of investigational product into either eye at the study visits. Samples that have been tested for positive binding antibodies may be further assessed for neutralizing antibodies. Additional blood samples may be obtained to rule out ADAs during the study.

The detection and characterization of antibodies to ABP 938 will be performed using a validated assay method by the sponsor or under the supervision of the sponsor.

6 Treatments

6.1 Investigational Product(s)

6.1.1 Description of Investigational Product(s)

Table 2 Investigational Product (ABP 938)

Name:	ABP 938
Dose(s):	2 mg (0.05 mL) administered every 4 weeks for the first 3 doses, followed by 2 mg (0.05 mL) once every 8 weeks
Mode of administration:	IVT injection

Table 3 Reference Product (Aflibercept)

Name:	aflibercept (Eylea®)
Dose(s):	2 mg (0.05 mL) administered every 4 weeks for the first 3 doses, followed by 2 mg (0.05 mL) once every 8 weeks
Mode of administration:	IVT injection

6.1.2 Preparation, Handling, and Storage

Refer to the Investigator Manual Clinical Trial Supply for full details regarding the preparation of ABP 938 and aflibercept.

The investigator (or designee) is responsible for the safe and proper storage of investigational product at the study center. ABP 938 and aflibercept will be stored under controlled conditions according to the storage requirements described on the labels and in the Investigator Manual Clinical Trial Supply.

6.1.3 Packaging, Labeling, and Shipment

ABP 938 and aflibercept will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice guidelines.

ABP 938 and aflibercept will be shipped and stored under controlled conditions according to the storage requirements.

Refer to the Investigator Manual Clinical Trial Supply for full details for packaging, labeling, and shipment of the investigational product.

6.1.4 Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

Any product complaint(s) associated with an ABP 938 or aflibercept supplied by Amgen are to be reported according to the instructions provided in the Investigator Manual Clinical Trial Supply.

6.1.5 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

Any nonstudy intraocular treatments, including macular photocoagulation or photodynamic therapy, long-acting intramuscular or intravenous corticosteroids (Exclusion Criterion **29**) are prohibited. Nonstudy aflibercept and ziv-aflibercept and any nonstudy intraocular or systemic anti-VEGF therapy are prohibited. Any experimental (biological or nonbiological) therapy (within or outside of a clinical study), except for the study drug, for subjects are prohibited. Subjects requiring these treatments will discontinue study treatment.

6.2 Masking

The study is double-masked; therefore, the investigators, study personnel, and the study subjects will remain masked to treatment allocation.

Randomization data will be kept strictly confidential, accessible only to authorized staff and the independent DMC until the time of unmasking. Authorized staff includes the randomization statistician, who will store the master randomization list in a secure system, an unmasked statistician, and unmasked programmers, who will provide the independent DMC with unmasked data for review, as and when required, in accordance with the procedures described in the DMC charter. All authorized unmasked staff must be documented. Personnel unmasked for the primary analysis will not be subsequently involved in study management.

ABP 938 and aflibercept will be coded and labeled in a manner that protects masking. The coding system will permit rapid identification of the product (in case of medical emergencies), that does not permit undetectable breaking of the mask.

Unmasking is only allowed in the case of an emergency, when knowledge of the investigational product is essential for the clinical management of the subject. The investigator must make every effort to contact the sponsor or designee's medical monitor prior to breaking the masking and must contact the sponsor or designee within 1 working day after the event, without revealing to the sponsor (or contract research organization [CRO]) the results of the code break, except to the designated global patient safety representative.

Emergency unmasking will be organized through the IXRS. The investigator must record the date of unmasking and the reason. All breaks of the masking must be adequately documented.

If a serious adverse event is reported, the designated global patient safety representative may unmask the treatment assignment for the individual subject through IXRS in order to meet regulatory reporting requirements.

6.3 Method of Assigning Treatment

Once the subject has met the criteria for enrollment and the investigator has determined that the subject is eligible, the subject will be randomized within the IXRS.

Randomization will be performed through a centralized IXRS. Eligible subjects will be assigned to ABP 938 or aflibercept in a 1:1 ratio. Each subject will receive a unique randomization number when he/she is assigned treatment. Subjects will be allocated to treatment according to the randomization code. The 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). 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. Each subject will receive a second randomization number when he/she is re-randomized.

6.4 Dose and Administration

Investigational product will be administered to the study eye at the times indicated in Table 1 via IVT by the Investigator (or qualified designee) under aseptic conditions and in accordance with the Eylea® product labeling. Anesthesia/analgesia and any other medication used for investigational product administration will be recorded in the CRF.

6.4.1 Dose Modification

No dose modifications are permitted during the study. However, investigational product dose(s) may be withheld if clinically necessary, in accordance with the current product labeling for Eylea® (eg, in case of rhegmatogenous retinal detachment, stage 3 or 4 macular hole, a subretinal hemorrhage involving the center of the fovea, or other reason per the product labeling).

If the subject presents with an infection at the dosing visit(s), the administration of investigational product may be delayed (up to 3 days for weeks 4 and 8, and up to 5 days for doses thereafter).

In the case of delayed or missed dose for any reason, subsequent doses should be administered according to the original schedule (ie, at the planned timepoint relative to first dose) investigational product dose(s).

6.4.2 Intervention After the End of the Study

After completing dosing with investigational product at week 48 and the follow-up visit at week 52, subjects will have completed the study. ABP 938 or aflibercept (Eylea®) will not be provided for poststudy use.

6.5 Treatment of the Fellow Eye

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

For subjects receiving neovascular (wet) AMD treatment in the fellow eye during the study, sites must request an additional box of investigational product from the IXRS to be dispensed for the fellow eye. The treatment dispensed for the fellow eye via the IXRS will be the same treatment type as the treatment received by the study eye. Other anti-VEGF treatments and investigational products (except for this study's investigational product) in the fellow eye are prohibited during the study.

Those subjects needing fellow eye treatment at Day 1 or week 4 should follow the same dosing schedule of the study eye (every 4 weeks ± 3 days).

Those subjects needing fellow eye treatment at **w**eek 8, 16, 24, 32, 40 and 48 should follow the same dosing schedule of the study eye (every 8 weeks ± 5 days).

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.

Safety assessments should be performed for the fellow eye at the fellow eye dosing days and at the end of study visit. Safety assessments include indirect ophthalmoscopy [assess predose only], slit-lamp [pre- and postdose], and intraocular pressure [pre- and postdose]), and the fellow eye should be monitored for safety events. Investigational product dosing data and safety data from the fellow eye administration should be captured in the CRF.

6.6 Precautions and/or Lifestyle Considerations

There are no lifestyle considerations (such as dietary or physical activity restrictions) for this study other than required contraception as listed in the inclusion/exclusion criteria (Section 4).

6.6.1 Coronavirus Disease 2019 Considerations

Study centers and subjects will follow local and institutional guidelines, as applicable, for the prevention of COVID-19 infection. In the event that a subject experiences any signs/symptoms of COVID-19, the subject should promptly notify the investigator.

6.7 Prior and Concomitant Therapy

6.7.1 Prior Treatment

Prior neovascular (wet) AMD therapies 1 month before randomization will be collected.

Prior non-neovascular (wet) AMD therapies that were being taken/used from 28 days prior to randomization will also be collected.

6.7.2 Concomitant Treatments (Medications and Therapies)

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.1.5.

All medication (including vaccines, over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken from 28 days before randomization until the end of the follow-up period/ end of study will be recorded in the appropriate section of the CRF.

The medical monitor should be contacted if there are any questions regarding prior or concomitant medication or procedures.

6.7.3 Prohibited Concomitant Medications

See Section 6.1.5.

6.7.4 Other Concomitant Medications and Treatments

Any other treatment (not explicitly excluded) considered necessary for the subject's welfare may be given at the discretion of the investigator. Administration of concomitant medications must be recorded.

All subjects who discontinue the investigational product should be offered alternative treatment if applicable. Treatment should be given according to normal clinical practice, after an EOS visit.

6.8 Compliance

Investigational product will be administered by the investigator or study center personnel, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and in the CRF. Treatment compliance will be assured by the reconciliation of all investigational product supplies and the site source documents by the Clinical Research Associate.

6.9 Accountability

The investigational product must not be used for any purpose other than that defined in this protocol. All supplies of investigational product will be accounted for in accordance with Good Clinical Practices (GCP). Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product during the study are provided in the Investigator Manual Clinical Trial Supply.

The pharmacist or (designee) should maintain accurate records of all investigational product supplies received during the study. These records should include the dates and amounts of investigational product that were received at the study center, dispensed, and destroyed or returned to the sponsor (or designee). The records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product and study subjects. If errors or damage in the investigational product shipments occur, the investigator should contact the sponsor (or its designee) immediately. Copies of the investigational product accountability records will be provided by each investigator for inclusion in the trial master file (TMF). The Clinical Research Associate will periodically check the supplies of investigational product held by the investigator or pharmacist to verify accountability of the investigational product used.

The investigator (or designee) will administer the investigational product only to the identified subjects in this study, according to the procedures described in this study protocol. Details of investigational product administered to subjects will be recorded in the CRF.

Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product received from the sponsor (or designee).

After the end of the study, all unused investigational product and all medication containers should be returned to the sponsor (or designee) for destruction or destroyed at the study center (if approved by the sponsor or designee). In either instance, complete documentation will be returned to the sponsor (or designee). The investigational product resupply will be managed by the IXRS.

7 Adverse Events

7.1 Definitions

7.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with the investigational product. An adverse event can therefore be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device, or procedure.

7.1.1.1 Events Meeting the Adverse Event Definition

Events that meet the adverse event definition are as follows:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with

possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae.

- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

7.1.1.2 Events NOT Meeting the Adverse Event Definition

Events not meeting the adverse event definition include:

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- A pre-existing condition that has not worsened during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an adverse event

7.1.2 Serious Adverse Events

A serious adverse event is defined as any untoward medical occurrence that meets at least 1 of the following serious criteria:

- Results in death (fatal)
- Life-threatening (places the subject at immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event

Definition of Terms

Life-threatening: the term "life-threatening" in the definition of "seriousness" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more

severe. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Hospitalization: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the adverse event should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

Disability/incapacity: The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Other medically important serious event: Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

7.1.3 Clinical Laboratory Abnormalities and Other Abnormal Assessments

The investigator is responsible for reviewing all laboratory test results, including review of laboratory test results prior to subject randomization and reviewing subsequent laboratory test results throughout the study. The investigator will determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. Laboratory abnormalities without clinical significance (based on the investigator's judgment) should not be recorded as adverse events or serious adverse events. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis abnormalities) that require medical or surgical intervention or lead to investigational product interruption, modification, or discontinuation must be recorded as an adverse event or serious adverse event, as applicable. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event. In addition, laboratory or other abnormal assessments (eg, in ECGs, vital signs) that are associated with signs and/or symptoms must be recorded as an adverse event or serious adverse event if they meet the definition of an adverse event or serious adverse event as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (eg, decreased hemoglobin).

7.1.4 Events of Interest

The EOIs will be defined in the Statistical Analysis Plan (SAP) and will be reviewed on an ongoing basis as part of safety monitoring. There are no additional expedited reporting requirements for EOIs, beyond what is defined for any adverse event report that qualifies to be expedited as part of regulatory reporting rules for investigational products.

7.2 Assessment of Adverse Events

7.2.1 Severity

The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on:

The Common Terminology Criteria for Adverse Events (CTCAE) version 4.03: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

7.2.2 Causality

The investigator is obligated to assess the relationship between investigational product and each occurrence of each adverse event/serious adverse event.

Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

The investigator will also consult the IB in his/her assessment.

For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.

The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

7.3 Documenting and Reporting Adverse Events

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur from the time of randomization through the EOS visit are recorded in subject's medical records as well as the applicable CRF Adverse Event Summary page. The adverse event grading scale to be used for this study will be the CTCAE version 4.03, as described in Section 7.2.1.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms)
- Dates of onset and resolution
- Severity (National Cancer Institute CTCAE version 4.03)
- Assessment of relatedness to investigational product, other protocol-required therapies or devices
- Action taken

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. A subject, or subject's legal guardian, can also voluntarily withdraw from treatment due to an adverse event. If the subject withdraws consent, the subject is encouraged to undergo, at a minimum, an EOS assessment.

It is the investigator's responsibility to review all documentation (eg, hospital notes, laboratory reports, and diagnostic reports) related to an adverse event. Wherever possible, the investigator's diagnosis, not the individual signs and symptoms, will be documented as the adverse event.

It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor or responsible CRO in lieu of completion of the CRF page.

If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be masked on the copies of the medical records before submission to sponsor or responsible CRO.

Investigators are not obligated to actively seek adverse events or serious adverse events after the subject's conclusion of study participation. However, if the investigator learns of any serious adverse event, including death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the investigational product or study participation, the investigator must promptly notify the sponsor.

7.4 Reporting of Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the ICF through the EOS visit are reported using the applicable CRF Adverse Event Summary page.

All serious adverse event must be collected, recorded and transmitted to Amgen, or its designee, within 24 hours following the investigator's knowledge of the event.

The investigator will submit any updated serious adverse event data to the sponsor or designee within 24 hours of it being available.

The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

If the electronic data capture (EDC) system is not functional, the serious adverse event can be reported by faxing a completed paper Serious Adverse Event Form or by direct telephone communication with Parexel at the numbers provided below. The event must be updated electronically in the EDC system by the clinical study center once the EDC function resumes.

Global reporting of SAEs (except Japan):

Phone (Safety line): +1 (781) 434-5010

NorthAmerica_Medical@parexel.com

Japan (Safety line): +81 3 6888 5377

After the study is completed at a given center, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. If a center receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the center can report this information on a paper Serious Adverse Event Form

7.4.1 Regulatory Reporting Requirements for Serious Adverse Events

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen, or its designee.

Prompt notification by the investigator to the sponsor (or designee) of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor (or designee) has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor (or designee) will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor (or designee) policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor (or designee) will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unmasked by Amgen or designee before submission to regulatory authorities. Aggregate analyses may also be unblinded by the Safety Assessment Team, as appropriate. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

7.5 Reporting of Serious Adverse Event After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after the end of the study. However, these serious adverse events can be reported to Amgen. Per local requirements in some countries,

investigators are required to report serious adverse events that they become aware of after the end of the study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical study cases and handled accordingly based on relationship to investigational product.

7.6 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

7.7 Adverse Event and Serious Adverse Event Follow-up

During the study the adverse events and serious adverse events should be followed proactively by the investigator at subsequent visits/contact. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or until the subject is lost to follow-up. At the time the subject's study participation ends, all ongoing adverse events and serious adverse events should be evaluated for resolution. All new or updated information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. New or updated information will be recorded in the originally completed Adverse Event CRF. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Adverse Event CRF.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen. If a subject dies during participation in the study, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology if available.

8 Statistics

8.1 General Procedures

All personnel involved with the analysis of the study will remain masked until database lock and identification of protocol deviations for the primary analysis. Personnel unmasked for the primary analysis will not be further involved in the management of the study. Analyses will be performed using SAS® version 9.4 or higher (SAS Institute, Cary, NC, US) by the sponsor or its representatives.

The SAP will be approved prior to lock of the study database and unmasking of the study data for the primary analysis. The SAP will provide a detailed description of the statistical methods and expand on the details provided in the protocol.

All data will be presented by treatment group. Descriptive statistics (number of observations, mean, standard deviation, median, minimum, and maximum) will be provided for continuous variables, and counts and percentages will be presented for categorical variables. Confidence intervals (CIs) may also be provided (when specified).

In general, baseline is defined as the last non-missing measurement/procedure before or on the date of first administration of investigational product.

8.2 Analysis Populations

The Full Analysis Set (FAS) will include all randomized subjects based on the treatment the subject is randomized to (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.

The Safety Analysis Set will include all subjects who receive at least 1 dose of investigational product and will be analyzed according to actual treatment received. This analysis set will be used for summaries of safety data, as well as immunogenicity data.

The Per Protocol 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 a 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. The analysis set will be analyzed according to actual treatment received in the study eye. This analysis set will be used for sensitivity analyses for the primary and key secondary efficacy endpoints.

The PK Analysis Set will include all subjects enrolled in the PK substudy who receive at least 1 dose of investigational product 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 the actual treatment received in the study eye.

8.3 Sample Size

Approximately 566 subjects (including at least 30 subjects from East Asia) 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 approximately 90% power to demonstrate equivalence at a 2-sided significance level of 0.025 with an equivalence margin of (-3.9, 3.9) on the primary efficacy endpoint of 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. In addition, the number of East Asian subjects (ie, 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.

8.4 Planned Analyses

The primary analysis of the study will be performed after all enrolled subjects reach week 24 or terminate early. The final analysis will be performed when all enrolled subjects complete the week 52 visit or terminate early.

8.5 Statistical Methods

8.5.1 Primary Endpoint/Estimand

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) 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.

Clinical equivalence will be evaluated using the FAS by comparing the 95% CI of the treatment difference between ABP 938 and aflibercept in the primary endpoint, change from baseline in BCVA at week 8, with an equivalence margin of (-3.9, 3.9) letters. The least squares (LS) mean difference between the 2 treatment groups and the corresponding 95% CI will be estimated using an analysis of covariance (ANCOVA) model for the week 8 BCVA change from baseline adjusted for region and baseline BCVA. Consistency in treatment effects between the East Asian subjects and the overall population will be evaluated by descriptive summaries and/or graphical displays.

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. Sensitivity analyses will be performed in the Per Protocol Analysis Set. **Sensitivity analyses will be conducted to evaluate the robustness of the result to potential departure from the MCAR assumption (see Section 8.5.10).**

8.5.2 Secondary Endpoint(s)

Secondary efficacy endpoints will be analyzed descriptively. BCVA, CNV, and CST changes from baseline will be summarized by visit. The LS mean differences and 95% CIs will be estimated using ANCOVA models similar to that used for the primary endpoint. Generalized linear models with identity link will be utilized to obtain the point estimate and 95% CIs for treatment differences in the following secondary endpoints: proportions of

subjects gaining ≥ 10 letters at week 8, maintaining vision at week 52, and gaining ≥ 15 letters at week 52.

Sensitivity analyses for the proportion of subjects who gained at least 10 letters of vision at week 8, CNV changes from baseline at week 8, and CST change from baseline at week 8 will be performed in the Per Protocol Analysis Set.

8.5.3 Safety Endpoint(s)

Safety analyses will focus on treatment-emergent adverse events. Treatment-emergent adverse events are defined as those that begin or increase in severity or frequency at or after the time of first treatment to the EOS visit.

Safety will be assessed descriptively in the Safety Analysis Set. Subject level safety data and safety data for the study eye will be summarized descriptively and separately for day 1 through week 8, day 1 through week 16, week 16 through the EOS visit, and day 1 through the EOS visit, based on actual treatment received in the study eye. The summaries for day 1 through week 8 and day 1 through week 16 will be presented by treatment (ABP 938 vs. aflibercept). The summaries for week 16 through the EOS visit and day 1 through the EOS visit will be presented by treatment sequence (ABP 938/ABP 938 vs. aflibercept/aflibercept vs. aflibercept/ABP 938) for subjects who are re-randomized and treated post re-randomization. For the subset of subjects who also have the fellow eye treated with the investigational product, their safety data collected for the fellow eye from the first investigational product treatment of the fellow eye to the EOS visit will be summarized similarly, and summaries will be based on the actual treatment received in the fellow eye. All reported adverse events will be assigned the system organ class and preferred term according to the Medical Dictionary for Regulatory Activities as of the time of the primary analysis and assessed for severity by CTCAE version 4.03. The number and percent of subjects reporting treatment-emergent adverse events (all, serious, and fatal) and EOIs will be tabulated.

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.

Vital signs and ophthalmoscopic assessments (indirect ophthalmoscopy, slit-lamp examinations, and IOP) will be presented by visit descriptively.

8.5.4 Demographic and Baseline Characteristics

Demographic characteristics (including age, sex, ethnicity, and race) and baseline characteristics (including height, weight, body mass index, and disease characteristics) will be presented by assigned treatment descriptively.

8.5.5 Exposure to Investigational Product

Exposure to ABP 938/aflibercept will be summarized descriptively at the subject level and separately for study eyes and fellow eyes for the different reporting periods specified for the safety analyses in Section 8.5.3.

8.5.6 Exposure to Concomitant Medications

Prior and concomitant medications will be coded using the latest available World Health Organization Drug Dictionary as of the time of the primary analysis and summarized descriptively.

8.5.7 Pharmacokinetic Endpoints

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

8.5.8 Immunogenicity Endpoints

The number and percentage of subjects developing ADAs will be tabulated by visit and by actual treatment received in the study eye for the different reporting periods specified for the safety analyses in Section 8.5.3. Only subjects who were re-randomized, and treated post re-randomization, and had a result post re-randomization will be included in the analyses for week 16 through the EOS visit. Subjects who were not re-randomized or were not treated post re-randomization will be excluded from the analyses for week 16 through the EOS visit and day 1 through the EOS visit.

8.5.9 Subgroup Analyses and Covariates

Consistency in treatment effects between the East Asian subjects and overall population will be evaluated descriptively by summaries and/or graphical displays.

Geographic regions and baseline BCVA letters, will be included in statistical models for the efficacy analyses as covariates. Additionally, subgroup analyses for efficacy endpoints may include geographic region and baseline BCVA category.

Full details of the subgroup analyses and covariates will be prespecified in the SAP.

8.5.10 Handling of Missing Values

For both the primary and secondary efficacy endpoints, the primary analysis will be based on observed data using the FAS; missing values will not be imputed. As a sensitivity analysis, missing data will be imputed by the last observation carried forward for the primary endpoint and non-response imputation for the binary secondary endpoints. A repeated-measures analysis for change from baseline in BCVA from day 1 through week 8 will also be performed assuming the data are missing at random. In addition, for the primary endpoint, tipping point analyses will be performed to explore the sensitivity of the results based on different assumptions for the missing data. Additional details are provided in the SAP.

Subjects who prematurely discontinue the study will be evaluated based on the data collected at each visit attended. Data collected during the withdrawal visit will be used as an EOS assessment for these subjects.

9 Ethics and Responsibilities

9.1 Good Clinical Practice

This study will be conducted in accordance with the protocol and with the Note for Guidance on International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Harmonised Tripartite Guideline E6 (R1)/Integrated Addendum E6 (R2); US Food and Drug Administration (FDA) Code of Federal Regulations (CFR) (Title 21 Parts 50, 56, 312), requirements for the conduct of clinical studies as provided in the EU Directive 2001/20/EC;

the general guidelines indicated in the Declaration of Helsinki; and all applicable laws and regulatory requirements.

9.2 Institutional Review Board/Independent Ethics Committee

Before initiating a study, the investigator/institution must have written and dated approval/favorable opinion from the IRBs/IECs for the study protocol/amendment(s), written ICF, any ICF updates, subject recruitment procedures (eg, advertisements), and any written information to be provided to subjects and a statement from the IRBs/IECs that these comply with GCP requirements (if applicable). A current copy of the IB should be included as part of the written application to the IRB/IEC.

A copy of the written approval of the protocol and ICF must be received by Amgen or designee before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. The IRB/IEC approval(s) must identify the protocol version as well as the documents reviewed. Any amendments to the protocol will require IRB/IEC approval before the implementation of the changes made to the study, except for changes necessary to eliminate an immediate hazard to the study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of serious adverse events or other significant safety findings, including adverse drug reactions (ADRs) that are both serious and unexpected, as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the study center and adherence to the requirements of all applicable regulations
- Promptly reporting deviations from, or changes to, the protocol to eliminate immediate hazards to the study subjects
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen or designee

9.3 Informed Consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the study, the investigator should have the IRB/IEC's written approval/favorable opinion of the written ICF and any other written information to be provided to subjects.

- The investigator or his/her representative will explain the purpose and nature of the study as well as possible adverse effects to the subject or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary, and consent can be withdrawn at any point.
- Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent.
- Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of US FDA CFR Title 21 Part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements where applicable, and the IRB/IEC or study center.
- Prior to a subject's participation in the study, the written ICF should be signed and personally dated by the subject or by the subject's legally authorized representative, and by the person who conducted the informed consent discussion.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. Subject withdrawal of consent or discontinuation from study, study treatment, and/or procedures must also be documented in the subject's medical records.
- The original copy of the signed ICF will be retained at the study center.
- A copy of the ICF and any other written information must be provided to the subject or the subject's legally authorized representative.
- If the ICF is revised, the revised ICF must have received the IRB/IEC's approval/favorable opinion in advance of its use. Subjects or legally authorized representative must be informed of the changes to the ICF and must re-consent to the most current version during their participation in the study. The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.
- The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The

investigator shall then inform the primary care physician. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

If a subject is unable to read or if a legally authorized representative is unable to read, an impartial witness should be present during the entire informed consent discussion. The witness should sign and personally date the ICF after:

- The written ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally authorized representative
- The subject or the subject's legally authorized representative has orally consented to the subject's participation in the study
- The subject or the subject's legally authorized representative has signed and personally dated the ICF, if they are capable of doing so

By signing the ICF, the witness attests that the information in the ICF and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally authorized representative, and that informed consent was freely given by the subject or the subject's legally authorized representative.

9.4 Data Monitoring Committee

A DMC will be formed with members consisting of individuals external to Amgen and the CRO chosen for their expertise in neovascular (wet) AMD. Members of the DMC will include, at a minimum, physicians and statistician(s). The primary role of this independent DMC will be to monitor safety data.

The DMC will review unmasked safety data at regular intervals beginning after approximately the first 16 subjects complete 2 doses (day 1 and week 4) of investigational product and approximately every 6-8 months thereafter, as outlined in the DMC charter.

In addition, the DMC will communicate any major safety concerns and recommendations regarding study modification or termination to Amgen senior management at any time during the conduct of the study.

Records of all meetings will be maintained by the CRO in a restricted, unmasked location for the duration of the study. Records of all meetings will be transferred and stored in the study

TMF at the conclusion of the study. Selected Amgen, or its designee, staff may serve as liaisons with the DMC, but will not be voting members. Personnel at Amgen or its designee involved in preparation or review of DMC unmasked materials will not be otherwise involved in the study. Details regarding the DMC will be provided in the DMC charter.

9.5 Financing and Insurance

9.5.1 Contractual and Financial Details

The investigator (and/or, as appropriate, the hospital administrative representative) and Amgen, or its designee, will sign a clinical study agreement prior to the start of the study, outlining overall Amgen, or its designee, and investigator responsibilities in relation to the study.

9.5.2 Insurance, Indemnity, and Compensation

Amgen will maintain an appropriate clinical study insurance policy. Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

9.5.3 Financial Disclosure

Investigators and subinvestigators will provide the sponsor or designee with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

10 Records Management

All clinical study information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. This principle applies to all records referenced in this protocol, irrespective of the type of media used.

A CRF will be used to store and transmit subject information. The CRF must be reviewed and electronically signed and dated by the investigator on an ongoing basis throughout the

study. The investigator is responsible for verifying that the data entries are accurate and correct by signing the CRF.

Access to the CRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the CRF completely by authorized site personnel (eg, investigators and the study coordinator). The CRF must be completed as soon as possible after any subject evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The CRFs and computers that store them must be accessible to Clinical Research Associates and other regulatory auditors. Changes to the CRF will be electronically tracked.

During each study visit, a physician participating in the study will maintain progress notes in the subject's medical records to document all significant observations. At a minimum, these notes are to contain:

- The date of the visit and the corresponding day or visit in the study schedule
- General condition and status remarks by the subject, including any significant medical findings. The severity, frequency, duration, and resolution of any reported adverse event, and the investigator's assessment as to whether or not the reported adverse event is related to investigational product
- Changes (including dosages) in concomitant medications/therapies (including over-the-counter medications and vitamins or dietary supplements) or procedures
- A general reference to the procedures completed
- The signature or initials of all physicians making an entry in the medical record (progress notes)

In addition, any contact with the subject by telephone or other means that provides significant clinical information is to also be documented in the medical record (progress notes), as described above.

Information from the medical records (progress notes) and other source documents is to be promptly entered into the appropriate section of the CRF.

Changes to information in the medical record (progress notes) and other source documents are to be initialed and dated on the day the change is made by the investigator (or

designee). If the reason for the change is not apparent, a brief explanation for the change is to be written adjacent to the change. Changes to the CRF will be electronically tracked.

The CRO data management department will write a Data Management Plan, which will be finalized prior to performing any data validation.

10.1 Source Documentation

Source documents contain the results of original observations and activities of a clinical investigation. They are the original records in which raw data are first recorded. Source documents include, but are not limited to, medical records (progress notes), ECG and computer printouts, screening logs, completed scales, and recorded data from automated instruments.

The investigator/site personnel should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's study subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, through an audit trail).

All source documents from this study are to be maintained by the investigator and made available for inspection by authorized persons. The investigator will provide direct access to source documents/data for study-related monitoring, audits, IRB/IEC review, and regulatory inspections. The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for study-related monitoring, audit, IRB/IEC review, and regulatory inspection.

10.2 Case Report Form Completion and Data Management

The file structure and format for the CRF will be provided by the sponsor or its representative and should be handled in accordance with the instructions provided.

Data will be entered/loaded into a validated electronic database using a clinical data management system. Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data.

10.3 Study Files and Record Retention

All data derived from the study will remain the property of the sponsor. The sponsor assumes accountability for actions delegated to other individuals, eg, the CRO.

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents, including records of subjects, source documents, CRFs, and the investigational product inventory, must be kept on file.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of ABP 938. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the sponsor. The sponsor is responsible for informing the investigator when these documents need no longer be retained.

The investigator is not to dispose of any records relevant to this study without written permission from the sponsor and is to provide the sponsor the opportunity to collect such records. The investigator shall take responsibility for maintaining adequate and accurate source documents of all observations and data generated during this study. Such documentation is subject to inspection by the sponsor, its representatives, and regulatory authorities.

If an investigator moves, withdraws from a study, or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the sponsor.

11 Auditing and Monitoring

Sponsor-assigned Clinical Research Associates will conduct regular monitoring of the investigational facilities for the purpose of monitoring various aspects of the study, such as assessing subject enrollment, compliance with protocol procedures, completeness and accuracy of data entered into the CRFs, verification of CRF data against original source documents, and occurrence of adverse events. The investigator must agree to sponsor-authorized personnel having direct access to the clinical (or associated) files and

clinical study supplies (dispensing and storage areas) to ensure compliance with applicable regulations, and the investigator will assist with the sponsor's monitoring activities.

Quality control will occur at each stage of data handling to ensure that all data are reliable and have been processed correctly. The sponsor should ensure oversight of any study-related duties and functions carried out on its behalf, including study-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

The CRFs should be completed in a timely manner and on an ongoing basis to allow regular review by the Clinical Research Associate.

Details describing the strategy, responsibilities, and requirements of the study monitoring are provided in the Study Monitoring Plan.

The purpose of an audit is to assess whether ethics, regulatory, and quality requirements are being fulfilled. The sponsor or its representative may conduct audits at the investigative centers including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of CRFs with source documents. Government regulatory authorities may also inspect the investigator during or after the study. The investigator (or designee) should contact the sponsor/CRO immediately if this occurs. All medical records (progress notes) must be available for audit. The investigator must agree to participate with audits conducted at a convenient time in a reasonable manner.

11.1 Risk and Quality Tolerance Limits

Perceived risks and quality tolerance limits (QTLs) will be identified and documented before the start of the study.

The sponsor and CRO will review risk control measures periodically to ascertain whether the implemented quality management activities remain effective and relevant. The quality management approach and any important deviations from the predefined QTLs (and remedial actions adopted) will be described in the clinical study report (CSR).

11.2 Protocol Adherence and Deviations

The investigator and site personnel should conduct the study in compliance with the protocol and should use continuous vigilance to identify and report protocol deviations.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol that may be on the part of the investigator, site personnel, or the subject.

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. For example, important protocol deviations may include enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the study.

The investigator should not implement any deviation from the protocol without agreement from the sponsor and prior review and approval from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard to a study subject, or when the change involves only logistical or administrative aspects of the study, such as a change in a monitor or telephone number.

In the event of an important protocol deviation, the investigator will discuss the deviation with the sponsor’s medical monitor and will come to an agreement as to whether the subject should be withdrawn from the study due to the important protocol deviation.

12 Amendments

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the sponsor.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC, and the investigator must await approval before implementing the changes. The sponsor or designee will submit protocol amendments to the appropriate regulatory authorities for approval.

The current version of the ICF will require similar modification if the IRB/IEC, investigator, and/or sponsor, judge the amendment to the protocol to substantially change the study design and/or increase the potential risk to the subject and/or impact the subject's involvement as a study subject. In such cases, the ICF will be renewed for enrolled subjects before their continued participation in the study.

13 Study Report and Publications

This study will be registered on ClinicalTrials.gov in accordance with applicable laws and publication policy, and may also be registered on other publicly accessible websites as necessary. The results of the study will be posted for public disclosure within 12 months of study completion.

The sponsor or designee is responsible for preparing and providing the appropriate regulatory authorities with the CSR according to the applicable regulatory requirements. The sponsor should ensure that the CSR meets the standards of the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3).

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review.

The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

14 Study Start and Termination

The study start date is the date on which the first subject is randomized to study.

The EOS date is defined as the date when the last subject across all centers is assessed or receives an intervention for evaluation in the study (ie, last subject visit) or has withdrawn prematurely, as applicable.

The sponsor reserves the right to terminate the study or the participation in the study at an investigator's center at any time. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

If the study is prematurely terminated or suspended for any reason, the sponsor/investigator/site personnel should promptly inform the study subjects and should ensure appropriate therapy and follow-up for the subjects. Where required by the applicable regulatory requirements, the IRB/IEC should be informed promptly and be provided with a detailed written explanation of the termination or suspension.

15 Confidentiality

All information generated in this study is considered confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the sponsor. However, authorized regulatory officials, IRB/IEC personnel, the sponsor, and the sponsor's authorized representatives are allowed full access to the records.

All study subjects must be informed that their personal study-related data will be used by the sponsor or designee in accordance with local data protection law. The level of disclosure must also be explained to the subject, who will be required to give consent for their data to be used as described in the ICF. The subjects must be informed that their medical records may be examined by auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Identification of subjects and CRFs shall be by unique subject identification numbers (such as subject identification number or randomization number only). All personal identifiers according to applicable regulations (eg, name, phone number) must be redacted permanently by the study center personnel and replaced with the subject's unique identification number in all records and data before transfer to the sponsor (or designee).

All personal details will be treated as confidential by the investigator and staff at the CRO.

16 References

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14. US FDA. Guidance for Industry: Quality considerations in demonstrating biosimilarity to a reference protein product. April 2015b, US FDA.

17 Appendices

17.1 Appendix I – Study Administrative Structure

Sponsor:	Amgen, Inc One Amgen Center Drive Thousand Oaks, CA USA 91320
Sponsor's medical expert	[redacted], MD, MPH **Vice President, Global Development-Biosimilars** Amgen, Inc
CRO's medical monitor:	[redacted], MD **Associate** Medical Director Parexel International (IRL) Limited **[redacted], MD** **Medical Director** **Parexel International (IRL) Limited** **[redacted] MD** **Associate Medical Director** **Parexel International (IRL) Limited**
CRO:	Parexel International (IRL) Limited

A log of the name and title of the investigators who are responsible for conducting the study, and the address and telephone numbers of the study centers will be maintained.

The names and addresses of any other laboratories involved in the study will be provided in the Investigator Laboratory Manual.

17.2 Appendix II - Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Male subjects and female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant or father a child during treatment and for 3 months after the last dose of protocol-required therapies.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.

- Premenarchal female
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Methods for Female Subjects

Acceptable Methods of Effective Contraception

- Combined (estrogen and progestogen containing) or progestogen-only hormonal methods given by oral, intravaginal, transdermal, injectable, or implantable route)
- Intrauterine device
- Intrauterine hormonal-releasing system
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject)
- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide
- Double barrier method: the male uses a condom and the female may choose either a cap, diaphragm, or sponge with spermicide (a female condom is not an option due to the risk of tearing when both partners use a condom)

Contraception Methods for Male Subjects

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with protocol-required therapies; the reliability of sexual abstinence must be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject)
- Use a condom during treatment and for an additional 3 months after the last dose of investigational product

The female partner should consider using an acceptable method of effective contraception such as: hormonal, intrauterine device, intrauterine hormonal-releasing system, female barrier method (diaphragm, cap, sponge [a female condom is not an option because there is a risk of tearing when both partners use a condom]).

Note: If the male's sole female partner is of nonchildbearing potential or has had a bilateral tubal ligation/occlusion, he is not required to use additional forms of contraception during the study.

Unacceptable Methods of Birth Control for Male and Female Subjects

Birth control methods that are considered unacceptable in clinical studies include:

- Periodic abstinence (calendar, symptothermal, postovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 3 months after the last dose of investigational product.
- Information will be recorded on the Pregnancy Notification Form. The form must be submitted to Amgen or its designee within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 3 months after the last dose of investigational product. This information will be forwarded to Amgen or its designee. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen or its designee, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen or its designee as a pregnancy exposure case.

- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a poststudy pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen or its designee. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment.

Male Subjects With Partners Who Become Pregnant

- In the event a male subject fathers a child during treatment, and for an additional 3 months after the last dose of investigational product, the information will be recorded on the Pregnancy Notification Form. The form must be submitted to Amgen or its designee within 24 hours of the center's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen or its designee.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen or its designee regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 3 months after the last dose of investigational product.
- Information will be recorded on the Lactation Notification Form and submitted to Amgen or its designee within 24 hours of the investigator's knowledge of event.

- Study treatment will be discontinued if female subject breastfeeds during the study as described in Exclusion Criterion 31.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 3 months after discontinuing protocol-required therapies.

PROTOCOL AMENDMENT 2 (23 MARCH 2021)

Amendment rationale

The protocol is being amended to adjust the assessments in the protocol based on site and regulatory feedback.

All content updates to the existing text in this protocol amendment are illustrated throughout in BOLD font and presented in this protocol summary.

Changes to the protocol version 2.0

- **Japan (Safety line) Telephone number has been updated.**
- **Number of global sites has been updated in the Synopsis.**
- **Footnotes "b, d, e, g, j, l, k" of Table 1 Schedule of Activities have been updated.**
- **Section 1.1.2 Non-Amgen Investigational Product (Aflibercept) has been updated to include additional adverse events reflected in the warnings and precautions section of the product labeling.**
- **Section 1.3 Benefit/ Risk Assessment has been updated to include a COVID-19 risk assessment.**
- **Section 2 Study Objective and Endpoints, one of the secondary efficacy endpoints has been updated.**
- **Section 3.1, Section 4.5.1, and Footnote "l" of Table 1 Schedule of Activities have been updated to include language with regards to the week 16 visit to ensure it is clear that a visit outside of the window is not allowed in.**
- **Section 3.1 Study Design has been updated to include information on PK substudy/on treatment of the fellow eye.**
- **Section 3.3.1 End-of-Study Definition, the definition of the primary completion date has been updated.**

- **Section 4.1 Inclusion Criteria and Section 4.2 Exclusion Criteria have been updated.**
- **Sections 4.3, 4.5.1, 4.5.2 and throughout have been updated to mention a legally authorized representative (previously referred to as legally acceptable representative).**
- **Sections 5.2.2, 5.2.3, 5.3.3, 5.3.4 and 5.3.5 have been updated to provide information on study visits.**
- **Section 5.3.2 Clinical Laboratory Evaluations has been updated to include information on additional local urine pregnancy tests.**
- **Section 5.3.8 Vital Signs has been updated.**
- **Section 5.4 Pharmacokinetics has been updated with information related to PK substudy.**
- **Section 5.5 Antidrug antibodies has been updated.**
- **Section 6.1.5 Excluded Treatments, Medical Devices, and/or Procedures during Study Period has been updated.**
- **Section 6.5 Treatment of the Fellow Eye has been updated.**
- **Section 6.6.1, a new section, Coronavirus Disease 2019 Considerations has been included.**
- **Section 6.7.1 Prior Treatment has been updated; to confirm that prior neovascular (wet) AMD therapies will now be collected 1 month before randomization.**
- **Section 8.5.8 Immunogenicity Endpoints has been updated.**
- **Section 7.4 Reporting of Serious Adverse Events has been updated with new a Japan Safety line.**
- **Section 8.5.8 Immunogenicity Endpoints has been updated.**

- **Section 11 Auditing and Monitoring has been updated based on remote monitoring visits.**

PROTOCOL AMENDMENT 1 (OCTOBER 2019)

Amendment rationale

The protocol is being amended to adjust the assessments in the protocol based on site feedback.

Changes to the protocol version 1.0

- **Number of study centers has been updated to 116.**
- **Section 4.1 Inclusion Criteria and section 4.2 Exclusion Criteria have been updated.**
- **Neovascular AMD has been updated to neovascular (wet) AMD for consistency.**
- **Section 5.2 Efficacy Assessments has been updated.**
- **Section 5.2.4 Fundus photography has been added as an efficacy assessment.**
- **Table 1 Schedule of Activities has been updated to reflect changes.**