CLINICAL STUDY PROTOCOL

Title:	An Open Label, Two-Arm Study in Subjects with Chorioretinal Vascular Disease to Evaluate ABP 938 and Aflibercept (Eylea®) in a Prefilled Syringe
Protocol Number:	20210034
Study Phase:	Phase 3B
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 91320-1799 (805) 447-1000
Contract Research Organization (CRO):	ICON Clinical Research South County Dublin Business Park, Leopardstown, Dublin 18, D18X5R3 Ireland Phone: +353-1-2912000 Fax: +353-1-2476260
Protocol Version and Date:	Version 1.0, 19 Oct 2022

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

NCT number: NCT05704725
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 Amgen and the investigator and must be documented in writing.

Amgen Inc. representative:

[redacted], MD, PhD	Executive Medical Director
Print Name	Title
Electronically signed by: [redacted] Reason: I am approving this document [redacted] Date: Oct 25, 2022 02:55 PDT	
Signature	Date

PROTOCOL SIGNATURE PAGE – CONTRACT RESEARCH ORGANIZATION

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

ICON Clinical Research representatives:

[redacted]	Medical Director
Print Name	Title
Electronically signed by: [redacted] MD [redacted] Reason: I am approving this document Date: Oct 25, 2022 10:19 GMT+2	
Signature	Date

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), 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 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 guidelines on Good Clinical Practice (ICH 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: myself (including, if applicable, my spouse or legal partner and dependent children) and my sub-investigators (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

SERIOUS ADVERSE EVENT CONTACT INFORMATION

In the event of a serious adverse event, the investigator will send a safety report form within 24 hours of becoming aware of the serious adverse event to Amgen Inc.

In the Americas:

Amgen Inc.
Fax: +1-888-814-8653
Email: svc-ags-in-us@amgen.com

Version 1.0, 19 Oct 2022
Initial creation

PROTOCOL SUMMARY

Protocol Number: 20210034

Protocol Title: An Open Label, Two-Arm Study in Subjects with Chorioretinal Vascular Disease to Evaluate ABP 938 and Aflibercept (Eylea®) in a Prefilled Syringe.

Sponsor: Amgen Inc.

Study Phase: Phase 3B

Indication: Chorioretinal vascular disease (CVD)

Study Sites: Approximately 4 sites in the United States (US).

Rationale: Amgen is developing ABP 938 as a biosimilar candidate to Eylea® (aflibercept). To administer ABP 938 as an intravitreal (IVT) injection, Amgen has also developed a prefilled syringe (PFS). The study will investigate whether the ABP 938 PFS can be used effectively and safely by retina specialists to administer the 2 mg dose of study drug, when descriptively compared to the US-licensed aflibercept PFS.

Objectives/Endpoints:

Objectives	Endpoints
Primary	
The primary objective for this study is to assess the ability of retina specialists to successfully administer, via an IVT injection, a 2 mg dose of ABP 938, using the ABP 938 PFS, compared to a 2 mg dose of aflibercept using the aflibercept PFS.	The primary endpoint for the study is the proportion of IVT injections successfully administered to subjects with CVD by retina specialists, utilizing the ABP 938 PFS or aflibercept PFS.
Secondary	
The secondary objective is to assess the safety of ABP 938 administered to subjects with CVD via an IVT injection, using the ABP 938 PFS compared to aflibercept administered using the aflibercept PFS.	The secondary endpoint for the study is the incidence of ocular adverse events (AEs) and serious adverse events (SAEs) in the study eye, and non-ocular SAEs until the end of study visit (Day 28 visit).

Study Design: This is an open label, two-arm, randomized, multi-site study within the US in adult subjects with CVD, including neovascular (wet) age-related macular degeneration (AMD), diabetic macular edema (DME), macular edema following retinal vein occlusion (RVO), or diabetic retinopathy (DR). Randomization will be stratified by retina specialist.

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

Study Procedures: After providing informed consent, subjects will be screened. After screening assessments are completed and if subject eligibility is confirmed, the subject will be enrolled into the study and randomized to either receive a single IVT injection of ABP 938 in a PFS or a single injection of aflibercept in a PFS and followed for safety events.

The use of the PFS will be evaluated by the ability of retina specialists to successfully administer the investigational product (IP) (test or reference product) 2 mg in PFS via IVT injections to subjects.

After completion of the IVT injection, the investigator will provide their assessment to report whether the injection was successfully administered or not.

Safety procedures for the study eye will include Best Corrected Visual Acuity (BCVA) by ETDRS (Early Treatment Diabetic Retinopathy Study), slit-lamp biomicroscopy, intraocular pressure (IOP), and indirect ophthalmoscopy and spectral domain- optical coherence Tomography (SD-OCT).

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

The start of the study will be the date on which the first subject provides informed consent, and the end of the study will be when the last subject has completed the assessments for the end of study visit. Whenever possible, all procedures listed under the end of study visit should be completed for subjects who are prematurely discontinued.

Planned Number of Subjects: Approximately 48 adult male or female subjects with a minimum of 32 subjects in the ABP 938 PFS arm and a minimum of 16 subjects in the aflibercept PFS arm (randomization ratio 2:1).

Target Population: Subjects aged ≥ 18 years old with treatment-naïve or previously treated neovascular (wet) AMD, DME, macular edema following RVO, or DR in the study eye, in whom treatment (IVT) with aflibercept is indicated.

Test Product:

Name: ABP 938

Dose: 2 mg/0.05 mL

Mode of administration: Single IVT injection using PFS

Reference Product:

Name: aflibercept

Dose: 2 mg/0.05 mL

Mode of administration: Single IVT injection using PFS

Statistical Methods: All analyses for this study will be summarized descriptively. The Full Analysis Set (FAS) will include all randomized subjects and will be analyzed according to randomized treatment. This analysis set will be used for summaries of the primary endpoint. The number and percentage of injections successfully administered utilizing the PFS will be provided descriptively separately by randomized treatment group. Percentages will be based upon the number of subjects in the FAS for each treatment group. The estimated primary endpoint success rate for each treatment group will be calculated by the average of each retina specialists' individual success rate.

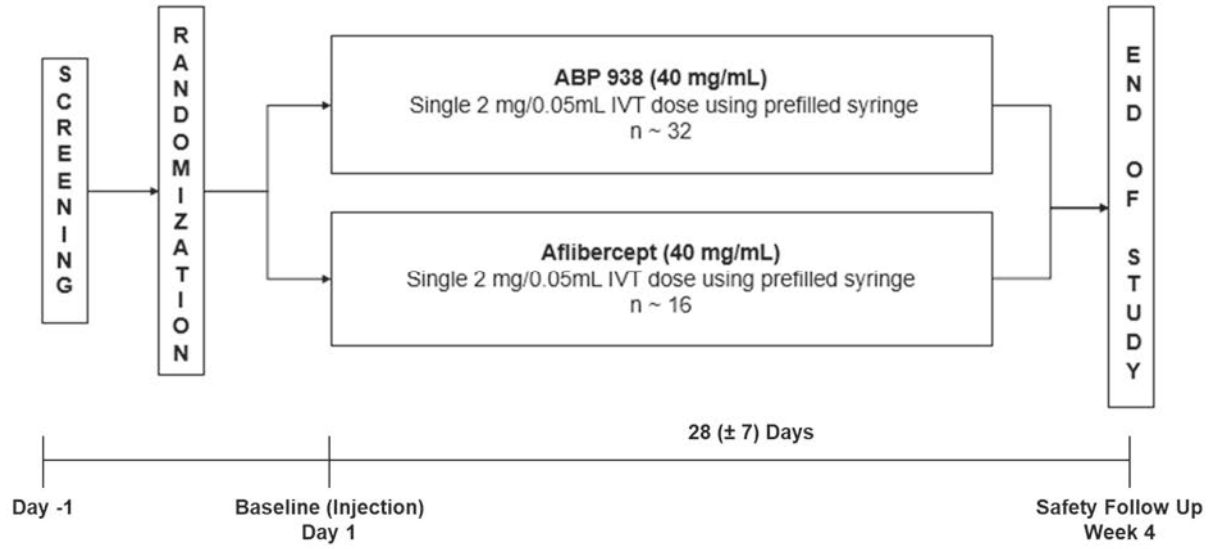
The Safety Analysis Set will include all randomized subjects who receive the IP and will be analyzed according to the actual treatment received. This analysis set will be used for summaries of safety data. All reported AEs will be assigned the system organ class and preferred term according to the Medical Dictionary for Regulatory Activities as of the time of analysis and graded by Common Terminology Criteria for Adverse Events, version 5.0. The number and percentage of subjects experiencing any ocular treatment emergent AEs (TEAEs) and serious treatment emergent adverse events (TE-SAEs) in the study eye, and non-ocular SAEs will be summarized descriptively and separately by actual treatment received.

Statistical Hypothesis: No formal statistical hypothesis testing will be conducted.

Protocol Version and Date: Version 1.0, 19 Oct 2022

STUDY SCHEMATIC

Figure 1 Study Schematic



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

SCHEDULE OF ASSESSMENTS

Table 1 Schedule of Assessments

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

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

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

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

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

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

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

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

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

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AMD	Age-related Macular Degeneration
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Chorioretinal Vascular Disease
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EOI	Events of Interest
FAS	Full Analysis Set
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HRT	Hormonal Replacement Therapy
IB	Investigator’s Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
IVT	Intravitreal
IXRS	Interactive Voice Response System / Interactive Web Response System

MedDRA	Medical Dictionary for Regulatory Activities
NCT	National Clinical Trial
PFS	Prefilled Syringe
PlGF	Placental Growth Factor
PT	Preferred Term
QTL	Quality Tolerance Limit
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TE-SAE	Treatment Emergent Serious Adverse Event
TMF	Trial Master File
US	United States
USPI	United States Prescribing Information
VEGF	Vascular Endothelial Growth Factor
WHODDE	World Health Organization Drug Dictionary Enhanced

1 Introduction and Rationale

1.1 Background

1.1.1 Disease

Chorioretinal vascular disease (CVD) constitutes the most common causes of moderate and severe vision loss in developed countries. These commonly include neovascular (wet) age-related macular degeneration (AMD), diabetic macular edema (DME), macular edema following retinal vein occlusion (RVO), and diabetic retinopathy (DR).[(1)]

AMD is a leading cause of blindness for people over the age of 65 in the United States (US). In the neovascular (wet or exudative) form of AMD, choroidal neovascular membranes disrupt the normal architecture of retina and adjacent tissues leading to retinal edema, submacular hemorrhage, as well as debilitating atrophy and scarring.[(2)]

The use of intravitreal (IVT) anti-vascular endothelial growth factor (VEGF) therapy is currently the standard of care for CVD. The anti-VEGF agents inhibit choroidal neovascularization growth and fluid leakage, which enable visual improvement.[(3)]

1.1.2 Amgen Test Product Background

Amgen is developing ABP 938 as a biosimilar candidate to Eylea® (aflibercept). ABP 938 belongs to the pharmacologic class of VEGF inhibitors and acts as a soluble decoy receptor that binds VEGF type A (VEGF-A), placental growth factor (PlGF), and to a lesser extent VEGF type B (VEGF-B), and thereby prevents binding and activation of VEGF receptor 1 (VEGFR1) and VEGF receptor 2 (VEGFR2).

1.1.3 Nonclinical Studies

A detailed summary of analytical and nonclinical data is provided in the Investigator's Brochure (IB).

1.1.4 Clinical Studies

A detailed description of the chemistry, pharmacology, efficacy, and safety of ABP 938 is provided in the IB. A Phase 3 study to assess effectiveness and safety of ABP 938 compared to aflibercept in subjects with neovascular (wet) AMD is currently ongoing.

1.1.5 Non-Amgen Reference Product

Aflibercept belongs to the pharmacologic class of VEGF inhibitors. In the US, it is approved for indicated IVT administration in the treatment of neovascular (wet) AMD, macular edema following RVO, DME, and DR.[(4)] 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

choroidal neovascularization (CNV).[5] Regeneron has developed a single dose prefilled syringe (PFS) for administration of aflibercept as an IVT injection.

1.2 Study Rationale

Amgen is developing ABP 938 as a biosimilar candidate to aflibercept. In an ongoing comparative clinical study ABP 938 is provided and used as a sterile aqueous solution for injection in single-use glass vials. Each vial used in that study provides a usable amount to deliver a single dose of 2 mg aflibercept in a volume of 50 µL. To administer ABP 938 as an IVT injection, Amgen has also developed a PFS. The study will investigate whether the ABP 938 PFS can be used effectively and safely by retina specialists, to administer the 2 mg dose of study drug, when descriptively compared to the US-licensed aflibercept PFS.

1.3 Benefit/Risk Assessment

ABP 938 is a biosimilar candidate to a reference product, aflibercept, for which the benefit-risk profile, following IVT administration for approved indications is well understood. A Phase 3 study to assess effectiveness and safety of ABP 938 compared to aflibercept in subjects with neovascular (wet) AMD is currently ongoing.

The 2 mg dose of both study drugs and administration via PFS in this study is consistent with the Eylea® prescribing information for subjects with CVD.

More detailed information about the known and expected benefits, risks, and reasonably expected AEs of ABP 938 and aflibercept can be found in the ABP 938 IB, and in the Eylea® United States Prescribing Information (USPI), August 2022, respectively.[4]

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 CVD.

Amgen closely monitors the Coronavirus disease 2019 (COVID-19) pandemic around the world. As part of this effort, Amgen performs a rigorous assessment, considering the study design, subject safety, public health risk, benefit-risk assessment, as well as the burden on country healthcare systems. Decisions are made on a study-by-study and country-by-country basis to minimize risk to subjects and avoid undue burden on healthcare facilities.

Subjects who display symptoms consistent with COVID-19 infections or who have tested positive for COVID-19 should contact the investigator to ensure appropriate care as well as documentation and management of study assessments.

Amgen considers that it is important to continue the proposed development of ABP 938 in this study in order to advance potential therapy options for subjects as rapidly as possible, while

balancing this with appropriate measures to monitor and mitigate the potential impact of COVID-19.

Study sites and subjects should follow the most recent local and institutional guidelines, as applicable, for the prevention of COVID-19 infection including COVID vaccinations. Based on general best practices for vaccination of immunocompromised individuals, it is recommended that the course of COVID-19 vaccinations is completed at least 2 weeks before study enrollment, or as per local guidance.

2 Objectives and Endpoints

Objectives	Endpoints
Primary	
The primary objective for this study is to assess the ability of retina specialists to successfully administer, via an IVT injection, a 2 mg dose of ABP 938, using the ABP 938 PFS, compared to a 2 mg dose of aflibercept using the aflibercept PFS.	The primary endpoint for the study is the proportion of IVT injections successfully administered to subjects with CVD by retina specialists, utilizing the ABP 938 PFS or aflibercept PFS.
Secondary	
The secondary objective is to assess the safety of ABP 938 administered to subjects with CVD via an IVT injection, using the ABP 938 PFS compared to aflibercept administered using the aflibercept PFS.	The secondary endpoint for the study is the incidence of ocular adverse events (AEs) and serious adverse events (SAEs) in the study eye, and non-ocular SAEs until the end of study visit (Day 28 visit).

3 Study Plan

3.1 Overall Study Design and Plan

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

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

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

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

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

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

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

The method of assigning subjects to treatment is discussed in Section 6.2.

No interim analyses are planned.

3.2 Discussion of Study Design

This is an open label, randomized study intended to assess if a PFS can be used effectively and safely by retina specialists to administer ABP 938. ABP 938 is intended to be developed as a biosimilar candidate to aflibercept which has been approved in many countries as an IVT injection for CVD. The dose of ABP 938 is the same as the reference product aflibercept. The secondary objective of the study is to assess ocular safety in the study eye and non-ocular SAEs.

3.3 End of Study

3.3.1 End of Study Definition

Primary completion/end of study: The primary completion date/end of study is the date when the last subject has completed the assessments for the end of study visit.

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

3.3.2 Study Duration for Subjects

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

4 Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. The study population will include men or women with treatment-naïve or previously treated neovascular AMD, DME, macular edema following RVO, or DR, in whom treatment with aflibercept is indicated.

4.1 Inclusion Criteria

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

1. The subject/subject's legally acceptable representative must sign an Institutional Review Board (IRB) approved ICF before any study-specific procedures are initiated.
2. Men or women ≥18 years old at screening.
3. Treatment-naïve or previously treated neovascular (wet) AMD, DME, macular edema following RVO, or DR in the study eye.

4.2 Exclusion Criteria

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

1. Active intraocular or periocular infection or active intraocular inflammation in either eye at baseline.
2. Uncontrolled intraocular pressure greater than (>) 25 millimeters of mercury (mmHg) in the study eye (uncontrolled defined as IOP > 25 mmHg despite intraocular pressure-lowering therapy).
3. Deemed legally blind in one or both eyes (count fingers or worse vision).
4. History of or any current indication of excessive bleeding or recurrent hemorrhages, including any prior excessive intraocular (including subconjunctival) bleeding or hemorrhages after IVT injection or intraocular procedures in either eye.
5. Current systemic infectious disease or on a therapy for active infectious disease.
6. History of any medical, ocular or non-ocular conditions that, in the opinion of the investigator, may interfere with the injection procedure or pose a safety concern.

7. History of stroke or transient ischemic attacks or myocardial infarction within the last 6 months prior to screening.
8. Treatment with anti-VEGF IVT injection in the study eye within 28 days prior to screening.
9. Any use of intraocular corticosteroids in the study eye within 3 months prior to screening.
10. Receipt of any systemic anti-VEGF within the last 6 months prior to screening.
11. Any invasive intraocular surgery, prior long-acting therapeutic agent, or ocular drug release device implantation (approved or investigational) in the study eye within the past 3 months prior to screening.
12. For women: pregnant or breast feeding, or planning to become pregnant while enrolled in the study and for 3 months after IP administration.
13. Sexually active subjects and their partners who are of childbearing potential (i.e., neither surgically sterile nor post-menopausal) who refuse to use adequate contraception (e.g., true abstinence, sterilization, injectable hormonal contraception, birth control pills, contraceptive implants, or other highly effective methods) while on-study and for 3 months after IP administration. Male subjects must agree not to donate sperm during study and for 3 months following dose of IP.
14. Allergy or hypersensitivity to the IP, to any of the excipients of ABP 938 or aflibercept, or to other study-related procedures/medications (e.g., anesthesia, antiseptic).
15. Previously enrolled in this study.
16. Participation in any interventional clinical study within 3 months prior to screening.

4.3 Subject Enrollment

Before subjects participate in any study-specific assessments/procedures, Amgen requires a copy of the site's written IRB approval of the protocol and ICF.

The subject or the subject's legally acceptable representative must personally sign and date the IRB and Amgen approved informed consent before the commencement of study-specific procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document the decision and date, in the subject's medical records.

Each subject will receive a unique 11-digit subject identification number obtained from the interactive web response system (IXRS). This will be assigned at the screening visit before

any study procedures are performed. The investigator will keep a record (the subject screening log) that includes limited information about the potential candidates (such as date of screening) for subjects who entered screening. The 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 unique 11-digit subject identification numbers will be assigned in sequential order for each site in the format 934XXXXX###, where “934XXXXX” refers to the site number, and ### refers to the sequential subject ordering as each subject at a site is entered into the IXRS system (i.e., 93412345001). If a subject withdraws from study participation, his/her unique identification number cannot be re-used for another subject.

The subject identification number must remain constant throughout the entire clinical study and must not be changed after initial assignment. This number will be different from the randomization number assigned for the study.

4.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but who do not meet did not meet entrance criteria required for participation and are not subsequently entered in the study. Data for subjects who fail screening will not be collected in the electronic data capture (EDC) system. Individuals who do not meet the criteria for participation in this study (screen failure) will not be rescreened.

4.5 Premature Discontinuation

Subjects have the right to withdraw from protocol procedures, or the study as a whole 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 Products

Subjects or their legally acceptable representative can decline to receive IP or undergo procedures but continue participation in the study. If this occurs, the investigator is to discuss with the subject the possibilities for continuation of the Schedule of Assessments (see Table 1) including different options of follow-up (e.g., 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, AEs, and device-related events and must document this decision in the subject’s medical records.

Subjects who have discontinued prior to or after receiving IP should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

Reasons for early removal from study or procedural assessments may include any of the following:

- Decision by Amgen.
- Lost to follow-up.
- Death.
- AE.
- Subject request.
- Pregnancy.

At the time of premature discontinuation, the subject should complete the assessments indicated at the end of study visit; see Table 1.

The study site will make every effort to ensure that subjects who receive ABP 938 or aflibercept, and subsequently prematurely discontinue the study complete the end of study visit.

4.5.2 Premature Discontinuation from the Study

Participation in the study is strictly voluntary. A subject 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:

- Difficulties conducting ophthalmic procedures.
- Violation of the protocol.
- Severe AEs or SAEs.
- Any other reason relating to the subject's safety or integrity of the study data.

If a subject is withdrawn from the study, the study monitor/Amgen will be informed immediately. Withdrawal of consent for a study means that the subject does not wish to receive IP or undergo procedures, and/or the subject does not wish to or is unable to continue further study participation. If there is a medical reason for withdrawal, the subject will remain under the supervision of the investigator until satisfactory health has returned.

If the subject withdraws consent for disclosure of further information, then Amgen may retain and continue to use any collected data before such a withdrawal of consent. Where permitted, publicly available data can be included after withdrawal of consent.

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 end of study visit; see Table 1.

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

For details on the discontinuation of study sites 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 site.

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

- The study site 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, 2 telephone calls and, if necessary, a certified letter to the subject’s last known mailing address or local equivalent methods).
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.
- For subjects who are lost to follow-up, the investigator can search publicly available records, where permitted, to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

5 Description of Study Assessments

Refer to Table 1 for the Schedule of Assessments.

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 approved informed consent before any study-specific procedures are performed.

5.1.2 Medical and Ophthalmic History

Medical and ophthalmic history, including any ongoing illnesses, will be collected.

5.1.3 Demographics

Demographic data, including year of birth/age, sex, and race, will be collected.

5.1.4 Urine Pregnancy

A urine pregnancy test will be performed for female subjects of child bearing potential at a local laboratory at the screening visit.

5.2 Assessment of Administration of Intravitreal Injection

The use of the PFS will be evaluated by the ability of retina specialists, to successfully administer the IP 2 mg in a PFS via IVT injections to a subject's study eye.

The preparation and administration of an ABP 938 or aflibercept IVT injection to dose subjects using a PFS will be guided by a list of tasks to be completed:

1. Firmly attach a 30 gauge needle (1/2 inch).
2. Carefully press/expel contents of the syringe to indicated line.
3. Perform IVT injection, injecting the full volume of drug.
4. Perform post injection safety check.

After completion of the injection, the investigator is required to provide their assessment to report whether the injection was successfully administered or not. If the response is no, a reason and details will be provided.

Refer to the pharmacy manual for detailed preparation and administration instructions.

5.3 Safety Assessments

The assessments described in the following sections will be performed for the study eye only.

5.3.1 Best Corrected Visual Acuity

The visual function of the study eye will be assessed prior to dilation at a distance of 4 meters at the screening and end of study visits using the Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA letter score.

5.3.2 Slit-Lamp Biomicroscopy

Slit-lamp biomicroscopy will be performed at the screening and end of study visits to assess the anterior eye structure prior to dilation.

5.3.3 Intraocular Pressure

IOP will be measured via applanation tonometry at the screening, baseline and end of study visits. For the baseline measurement, IOP will be measured pre-dose (prior to dilation) and 15-60 minutes after IP administration. The method of IOP measurement should be consistent for each subject throughout the study.

5.3.4 Indirect Ophthalmoscopy

Indirect ophthalmoscopy for evaluating the posterior segment will be assessed and reported at the screening, baseline, and end of study visits. For the baseline assessment, the indirect ophthalmoscopy will be performed pre-dose and after IP administration.

5.3.5 Spectral Domain Optical Coherence Tomography

SD-OCT will be performed at the screening and end of study visits to assess the structure of the retina. The same device should be used for a subject throughout the study.

5.3.6 Adverse Events

AEs are defined in Section 7.1.1. AEs will be followed, collected, and reported in line with the procedures described in Section 7.3.

5.3.7 Pregnancy

Details of all pregnancies and/or lactation in female subjects and pregnancies in male subjects' partners will be collected after the start of study treatment and until the end of study visit.

If pregnancy/lactation is reported, the investigator must inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Section 17.3. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Further details regarding pregnancy and lactation are provided in Section 17.3.

6 Treatments

6.1 Investigational Products

6.1.1 Description of Investigational Products

Test Product

Name:	ABP 938
Dose:	2 mg/0.05 mL
Mode of administration:	Single IVT injection using PFS
Manufacturer:	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320-1799

Reference Product

Name:	aflibercept
Dose(s):	2 mg/0.05 mL
Mode of administration:	Single IVT injection using PFS
Manufacturer:	Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591

6.1.2 Handling and Storage

ABP 938 and aflibercept should be stored according to the storage information provided on the IP carton. The PFS should be stored in a refrigerator (2° to 8°C) and protected from light. Further details regarding handling and storage are provided in the IB and the pharmacy manual.

6.1.3 Packaging, Labeling, and Shipment

Open label ABP 938 and aflibercept will be packaged and labeled in accordance with all applicable regulatory requirements. ABP 938 and aflibercept will be shipped at a temperature of 2ºC to 8ºC and stored under controlled conditions according to the storage requirements.

Refer to the IB and pharmacy manual for full details for packaging, labeling, and shipment of the IP.

Amgen will supply ABP 938 and aflibercept as PFSs.

6.1.4 Product Complaints

Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic by either: (1) Amgen or (2) distributors or partners for whom Amgen manufactures the material. This includes all components distributed with the drug, such as packaging, drug containers, delivery system, labeling, and inserts.

Any product complaint(s) associated with an investigational product, non-investigational products, devices, or combination products supplied by Amgen are to be reported according to the instructions provided in the pharmacy manual.

6.2 Method of Assigning Treatment

Once the subject has successfully met the criteria for enrollment the subject will be confirmed as enrolled within the IXRS.

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

6.3 Dose and Administration

ABP 938 and aflibercept 2 mg/0.05 mL will be administered as a single IVT injection.

6.3.1 Intervention After the End of the Study

There are no planned interventions following the end of the study.

6.4 Precautions and/or Lifestyle Considerations

There are no lifestyle considerations (such as dietary or physical activity restrictions) for this study further to those listed in the inclusion/exclusion criteria (Section 4).

6.5 Prior and Concomitant Therapy

All medication (including vaccines, over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken from 30 days before the start of screening until the end of study visit will be collected.

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

6.5.1 Prior Treatment (Medications and Therapies)

Prior therapies, defined as those that were stopped at or within 30 days prior to the baseline visit, will be collected.

6.5.2 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 described in Section 6.5.3.

Concomitant therapies are to be collected from screening until the end of study visit. Concomitant therapies are defined as those that are ongoing at the time of IP administration and during the follow-up period. Generic names for concomitant medication should be used, if possible.

All subjects who do not receive IP should be offered alternative treatment, if applicable. Treatment should be given according to normal clinical practice after the end of study visit.

6.5.2.1 Concomitant Treatment of the Fellow Eye

Standard-of-care treatment will be allowed for any ocular condition in the fellow eye at any time during the study. At the discretion of the qualified specialist, the subject's fellow eye may receive treatment on the same day as the study eye or at an unscheduled visit. All fellow eye treatments must be collected on the electronic case report form (eCRF) as a concomitant medication and/or procedure for the fellow eye. The fellow eye will not be considered an additional study eye. Subjects who receive treatment for the fellow eye will not be required to be withdrawn from the study.

6.5.3 Prohibited Concomitant Medications and Procedures

Subjects may not receive any medications (approved or investigational) in the study eye other than the assigned study treatment as specified in this protocol, unless they have completed the end of study visit assessments.

This includes medications administered locally (e.g., IVT, topical, juxtascleral or periorbital routes), as well as those administered systemically, with the intent of treating the study eye.

6.5.4 Rescue Medication

Although the use of rescue medications is allowed at any time during the study, the use of rescue medications should be delayed, if possible. The date and time of rescue medication administration, as well as the name and dosage regimen of the rescue medication, must be collected.

6.6 Overdose

The ABP 938 and aflibercept PFS are designed to deliver a single dose of 2 mg drug in a volume of 0.05 mL, therefore, the chances of overdose with a single IVT injection are minimal.

Overdosing of ABP 938 and aflibercept may increase intraocular pressure. Therefore, in case of overdose, intraocular pressure should be monitored and, if deemed necessary by the investigator, adequate treatment should be initiated.

6.7 Compliance

Subjects will be administered the IP by the investigator in a single dose on Day 1. Treatment compliance will be assured by the investigator who will record the date and time of each dose administered in the clinic in the source documents.

6.8 Accountability

The IP must not be used for any purpose other than that defined in this protocol. All supplies of IP will be accounted for in accordance with GCP.

The pharmacist or (designee) should maintain accurate records of all IP supplies received during the study. These records should include the dates and amounts of IP that were received at the study site, dispensed, and destroyed on site following guidance in the pharmacy manual. The records should include dates, quantities, lot numbers, expiration dates, and subject numbers. If errors or damage to the IP shipments occur, the investigator should contact Amgen (or its designee) immediately. Copies of the IP accountability records will be provided by each investigator for inclusion in the trial master file (TMF) after database lock. The study monitor will periodically check IP supplies held by the investigator or pharmacist to verify accountability of the IP used.

The investigator (or designee) will administer the IP only to the identified subjects in this study, according to the procedures described in this study protocol. Investigators should maintain records that adequately document that the subjects were provided the dose specified by the protocol and reconcile all IP received from Amgen (or designee).

After the end of the study, all unused IP and all medication containers should be destroyed at the study site and complete documentation will be returned to Amgen.

7 Adverse Events

7.1 Definitions

7.1.1 Adverse Events

An AE is any untoward medical occurrence in a clinical study subject. The event does not necessarily have a causal relationship with the IP. The investigator is responsible for ensuring

that any AEs observed by the investigator or reported by the subject are recorded in the subject's medical records as well as in the eCRF.

The definition of AEs includes worsening of a pre-existing medical condition. Worsening indicates that a pre-existing medical condition (e.g., diabetes, migraine headaches, and gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. In the case of worsening of a pre-existing condition, the start date of the event is the date when the first signs of worsening were observed. 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 AE.

Note: an AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) in the investigator's opinion, is 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 AE definition are as follows:

- Any abnormal or worsening ocular safety result that is considered clinically significant in the medical and scientific judgment of the investigator.
- 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 overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae.

7.1.1.2 Events NOT Meeting the Adverse Event Definition

Events not meeting the AE definition include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- 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.

7.1.2 Serious Adverse Events

An SAE is any event that meets at least 1 of the following serious criteria:

- 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: an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred. 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 AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Hospitalization: an AE requiring hospitalization should be considered as an SAE. Hospitalization for elective surgery, or for procedures planned prior to the subject providing informed consent, or routine clinical procedures that are not the result of an AE (e.g., elective surgery for a pre-existing condition that has not worsened) should not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'nonserious' according to the usual criteria. An AE would meet the criterion of “requires hospitalization”, if the event necessitated an admission to a health care facility (e.g., overnight stay). When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Complications that occur during hospitalization are an AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious.

Disability/incapacity: an AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject’s ability to carry out 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 (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Other medically important serious event: If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a SAE under the criterion of "other medically important serious event." Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury, or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

7.1.3 Suspected Unexpected Serious Adverse Reactions

A suspected unexpected serious adverse reaction (SUSAR) is defined as an untoward and unintended response to a IP, which is not listed in the applicable product information, and meets one of the following serious criteria: results in death, is life-threatening, requires hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect; and is assessed as causally related to the IP.

7.1.4 Other Abnormal Assessments

Where applicable, the investigator is responsible for reviewing other assessments and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. Where applicable, clinical sequelae are to be recorded as the AE. In addition, abnormal assessments that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2.

7.1.5 Events of Interest

The adverse events of interest (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 AE report that qualifies to be expedited as part of regulatory reporting rules for IPs.

7.1.6 Adverse Device Effects

The detection and documentation procedures for adverse device effects described in this protocol apply to all ABP 938 and aflibercept PFSs provided for use in the study.

An adverse device effect is any AE related to the use of a combination product or medical device. Adverse device effects include AEs resulting from insufficient or inadequate instructions for use, AEs resulting from any malfunction of the device, or AEs resulting from use error or from intentional misuse of the device.

In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of any adverse device effects that occur during the study with such devices.

All adverse device effects are to be reported as AEs following the same reporting periods and procedures.

Product complaints are described in Section 6.1.4.

7.2 Assessment of Adverse Events

7.2.1 Severity

The terms serious and severe are not synonymous. The general term “severe” is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a grade 3 headache). This is NOT the same as serious, which is usually associated with events that pose a threat to a subject’s life or ability to function (see Section 7.1.2). A severe AE (classified as grades 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000/mm^3 is considered grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

The investigator will make an assessment of severity for each AE and SAE reported during the study using the CTCAE, version 5.0.

7.2.2 Causality

- The investigator is obligated to assess the relationship between the IP and each occurrence of an AE/SAE.
- Relatedness means that there are facts or reasons to support a relationship between the IP and the event.
- The investigator will use their 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 and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which a SAE 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 SAE data.

- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
- A causal relationship is indicated by a “yes” or “no” response to the question: “Is there a reasonable possibility that the event may have been caused by the IP?”.

7.3 Documenting and Reporting Adverse Events

The investigator is responsible for ensuring that all AEs observed by the investigator or reported by the subject that occur from the signing of the ICF until the end of study visit using the applicable eCRF Adverse Event Summary page.

Occurrence of AEs may be volunteered spontaneously by the subject; discovered as a result of general, non-leading verbal questioning by the study staff; or determined by physical examination or other safety assessments.

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator must assign the following AE attributes:

- AE diagnosis or syndrome(s), if known (if not known, signs or symptoms).
- Dates of onset and resolution.
- Severity.
- Assessment of relatedness to the IP, or devices.
- Action taken.

The investigator’s clinical judgment is used to determine whether a subject should be removed from treatment due to an AE. A subject, or subject’s legally acceptable representative, can also voluntarily withdraw from treatment due to an AE. If the subject withdraws consent, the subject is encouraged to undergo, at a minimum, an end of study assessment.

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

It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor/responsible contract research organization (CRO) in lieu of completion of the Event eCRF 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 blinded on the copies of the medical records before submission to Amgen.

Investigators are not obligated to actively seek AEs or SAEs after the subject's conclusion of study participation. However, if the investigator learns of any SAE, 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 IP or study participation, the investigator must promptly notify Amgen.

7.4 Reporting of Serious Adverse Events

The SAE must be reported to Amgen, or its designee, within 24 hours following the investigator's knowledge of the event using the paper Serious Adverse Event Report Form.

The investigator will submit any updated SAE data to Amgen within 24 hours of it being available.

The SAE can be reported by faxing a completed paper Serious Adverse Event Fax Cover Sheet and Serious Adverse Event Report Form at the number provided below.

Fax information to Safety Risk Management/ICON, for the attention of:

In the Americas:

Amgen Inc.

Fax: +1-888-814-8653

Email: svc-ags-in-us@amgen.com

In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the Serious Adverse Event Report Form sent by overnight mail or courier service.

Initial notification via telephone does not replace the need for the investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the SAE must be consistent with that recorded on the applicable eCRF (e.g., Adverse Event Summary eCRF).

If a subject is permanently withdrawn from study because of an SAE, this information must be submitted to Amgen, or its designee.

Investigators will receive notification of related SAE reports sent to regulatory authorities in accordance with local requirements.

Determination of expectedness for Amgen products will be based on the IB for the IP and the regional prescribing information for products being studied for an approved use. Expectedness assessments are to be made for all IPs (Amgen and non-Amgen) using the appropriate reference safety information per local regulatory reporting requirements. SUSARs reported for subjects receiving a non-Amgen IP are to be expedited according to local requirements.

Amgen, or its designee, reports SAEs and/or SUSARs as required to regulatory authorities, investigators/institutions, and IRBs in compliance with all reporting requirements according to local regulations and GCPs.

The investigator is to notify the appropriate IRB of SAEs occurring at the study site and other AE reports received from Amgen, in accordance with local procedures and statutes.

After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for SAEs. However, if the investigator becomes aware of a SAE after this protocol-required reporting period, the investigator will report the event to Amgen within 24 hours following the investigator's knowledge of the event. SAEs reported outside of the protocol-required reporting period will be captured within the safety database as clinical study cases for the purposes of expedited reporting.

7.5 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence.

7.6 Adverse Event and Serious Adverse Event Follow-up

During the study AEs, EOIs and SAEs should be followed proactively by the investigator until the event resolves, or the condition stabilizes to a level acceptable to the investigator, 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 related SAEs should be evaluated for resolution.

7.7 Safety Reporting Oversight

In accordance with ICH GCP, Amgen (or designee) will inform investigators of "findings that could affect adversely the safety of subjects, impact the conduct of the study, or alter the IRB's approval/favorable opinion to continue the study."

An investigator who receives an investigator safety report describing SAEs or other specific safety information (e.g., summary or listing of SAEs) from Amgen will file it along with the IB and will notify the IRB, if appropriate, according to local requirements.

Prompt notification by the investigator to Amgen of SAEs 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. Amgen 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. Individual safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8 Statistics

8.1 General Procedures

Analyses will be performed using SAS® (SAS Institute, Cary, NC, US) by Amgen or its representatives.

The SAP will be approved prior to first subject first visit. 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 [SD], median, minimum, and maximum) will be provided for continuous variables, and counts and percentages will be presented for categorical variables. Confidence intervals for the primary endpoint will also be presented.

Baseline is defined as the last non-missing measurement before IP administration.

8.2 Analysis Populations

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

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

8.3 Sample Size

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

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

8.4 Planned Analyses

8.4.1 Interim Analysis and Early Stopping Guidelines

No interim analysis is planned for this study.

8.4.2 Final Analysis

The final analysis of the study will occur when all subjects completed the day 28 visit or terminate early.

8.5 Statistical Methods

8.5.1 Primary Endpoint

The primary endpoint of the number of successful IP injections with the PFS will be summarized using the FAS based on observed data. The number and percentage of injections successfully administered utilizing the PFS will be provided descriptively for separately by randomized treatment group. Percentages will be based upon the number of subjects in the FAS for each treatment group. The estimated primary endpoint success rate for each treatment group will be calculated by the average of each retina specialists' individual success rate. The variance of this estimator will be calculated as:

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

where p_i is the proportion of successfully IVT injections administered for the i-th retina specialist and $\bar{p}$ is the average of proportions of successfully administered IVT injections across all retina specialists, K is the total number of retina specialists. T-distribution with (K-1) degrees of freedom will be used to calculate any corresponding confidence interval. No formal statistical comparisons will be performed between the two treatment groups. Missing data will not be imputed.

8.5.2 Secondary Endpoints

The secondary endpoints of ocular treatment emergent adverse events (TEAEs) and serious TEAEs (TE-SAEs) in the study eye and non-ocular TE-SAEs will be summarized with qualitative descriptive statistics for all subjects and separately by actual treatment received using the Safety Analysis Set.

For each secondary endpoint, the total number of TEAEs and the number and percentages of subjects experiencing at least one TEAE will be summarized for all subjects and by actual treatment received. Summaries will also include the number and percentages of subjects experiencing at least one TEAE within a System Organ Class (SOC) and Preferred Terms

(PTs) within SOCs. Subjects with multiple TEAEs will be counted only once within each PT and SOC.

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

TEAEs are defined as AEs with an onset after IP administration.

8.5.3 Safety Endpoints

The Safety Analysis Set will be used for the analysis of all safety data. Only TEAEs will be summarized.

An overall summary table of AEs will be presented which will include breakdowns of ocular TEAEs in the study eye, non-ocular TEAEs, TE-SAEs, TEAEs leading to study discontinuation, TEAEs leading to death, treatment related TEAEs, EOIs, etc. The number and percentage of subjects experiencing at least one event will be presented. Details of the overall summary table of AEs will be addressed in the SAP. Additional summaries of AEs by SOC and PTs by maximum severity may include ocular TEAEs in the study eye/fellow eye, injection procedure related ocular TEAEs in the study eye, etc.

Quantitative safety assessments such as BCVA using ETDRS and IOP will be summarized at each time point and visit using continuous descriptive statistics for the study eye for all subjects and actual treatment received. Change from baseline, calculated as post-baseline value minus baseline value, will be summarized at each scheduled post-baseline assessment.

Qualitative safety assessments such as slit-lamp biomicroscopy and indirect ophthalmoscopy will be summarized using counts and percentages for the study eye for all subjects and actual treatment received. Shifts from baseline will also be presented at each scheduled post-baseline assessment.

Subject listings will be generated for all SAEs all safety assessments.

8.5.4 Demographic and Baseline Characteristics

Demographic characteristics (including age, sex, ethnicity, and race) and baseline characteristics will be presented by assigned treatment descriptively for the FAS and the safety analysis set.

8.5.5 Exposure to Investigational Products

Subject exposure to IP will be analyzed using the safety analysis set.

8.5.6 Exposure to Concomitant Medications

Prior and concomitant medications used in this study will be coded using the latest available version of the World Health Organization Drug Dictionary Enhanced (WHODDE). The dictionary version will be detailed in the SAP. Concomitant medications will be summarized for the safety analysis set.

8.5.7 Handling of Missing Values

Missing primary endpoint will not be imputed. Missing safety data will generally not be imputed. Missing dates for AEs, medical history, and concomitant medications may be imputed for the purposes of TEAE flags, concomitant flags, etc. Rules for imputation of missing dates will be detailed in the SAP.

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 GCP ICH Harmonised Tripartite Guideline E6 (R1)/Integrated Addendum E6 (R2); US FDA 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 regulatory requirements.

9.2 Institutional Review Board

Before initiating a study, the investigator/institution must have written and dated approval/favorable opinion from the IRBs for the study protocol/amendment(s), written ICF, any ICF updates, subject recruitment procedures (e.g., advertisements), and any written information to be provided to subjects and a statement from the IRBs 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.

Amgen may amend the protocol at any time. A copy of the written approval of the protocol and ICF must be received by Amgen before recruitment of subjects into the study and IP shipment.

The IRB approval(s) must identify the protocol version as well as the documents reviewed. Any amendments to the protocol will require IRB/ 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 annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
- Notifying the IRB of SAEs or other significant safety findings, including adverse drug reactions (ADRs) that are both serious and unexpected, as required by IRB procedures.
- Providing oversight of the conduct of the study at the study site 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 approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB continuance of approval must be sent to Amgen.

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. Both the informed consent discussion and the written ICF and any other written information to be provided to subjects should include explanations of the following:

- 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 acceptable 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 acceptable 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's or study site.
- 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 acceptable 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 site.
- A copy of the ICF and any other written information must be provided to the subject or the subject's legally acceptable representative.
- If the ICF is revised, the revised ICF must have received the IRB's approval/favorable opinion in advance of its use. Subjects 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 acceptable 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 records.

9.4 Financing and Insurance

9.4.1 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. The contract should describe whether costs for pharmacy, laboratory, and other protocol-required services are being paid directly or indirectly.

9.4.2 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.

9.4.3 Financial Disclosure

Investigators and sub-investigators will provide Amgen with sufficient, accurate financial information as requested to allow Amgen to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

10 Records Management

All clinical study information should be collected, 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.

An eCRF will be used to store and transmit subject information. The eCRF 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 eCRF.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by authorized site personnel (e.g., investigators and the study coordinators). The eCRF 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 eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors. Changes to the eCRF will be electronically tracked.

During each study visit, the investigator 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 AE, and the investigator's assessment as to whether or not the reported AE is related to the IP.
- Changes (including dosages) in concomitant medications/therapies 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 should be documented in the medical record (progress notes), as described above.

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

Changes to information in medical records (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.

The ICON 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 collected. Source documents include, but are not limited to, medical records (progress notes), computer printouts, screening logs, and drug dispensing/accountability logs, etc.

The investigator/site personnel should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study site'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 (e.g., 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 review, and regulatory inspections. Amgen should verify that each subject has consented, in writing, to direct access to his/her original medical records for study-related monitoring, audit, IRB review, and regulatory inspection. The original signed ICF for each subject shall be filed with records kept by the investigator and a copy shall be given to the subject.

10.2 Case Report Form Completion and Data Management

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

The eCRF must be reviewed and electronically signed and dated by the investigator.

Changes to the eCRF will be electronically tracked.

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 Amgen. Amgen assumes accountability for actions delegated to other individuals, e.g., 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, eCRFs, and the IP 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 Amgen. Amgen 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 Amgen and is to provide Amgen the opportunity to collect such records. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by Amgen, 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 Amgen.

11 Auditing and Monitoring

Auditing

Amgen or its representative may conduct audits at the sites including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. All medical records (progress notes) must be available for the audit. The investigator must agree to participate with audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also inspect the site during or after the study. The investigator (or designee) should contact Amgen/CRO immediately if this occurs.

The purpose of an audit is to assess whether ethics, regulatory, and quality requirements are being fulfilled.

Monitoring

Sponsor-assigned monitors will conduct regular site visits at the site 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 eCRFs, verification of eCRF data against original source documents, and occurrence of AEs. 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 Amgen'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. Amgen 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 Amgen's contracted CRO(s).

The eCRFs should be completed in a timely manner and on an ongoing basis to allow regular review by the study monitor.

Details describing the strategy, responsibilities, and requirements of the study monitoring are provided in the clinical management plan.

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.

Amgen 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.

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 Amgen and prior review and approval from the IRB 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 Amgen’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 Amgen. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately.

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

The current version of the ICF will require similar modification if the IRB, 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

Amgen is responsible for preparing and providing the appropriate regulatory authorities with the CSR according to the applicable regulatory requirements. Amgen 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 governance and responsibilities of which are set forth in a Publication Charter. The committee

is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. 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, multi-site 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 (e.g., 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 provides informed consent.

The end of the study date is the date when the last subject has completed the assessments for the end of study visit.

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

Both Amgen and the investigator reserve the right to terminate the study or the participation in the study at an investigator’s site at any time. In terminating the study, Amgen 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, Amgen/investigators/site personnel should promptly inform the study subjects and should assure appropriate therapy and follow-up for the subjects. Where required by the applicable regulatory requirements, the IRB should be informed promptly and be provided with a detailed written explanation of the termination or suspension.

If the investigator terminates or suspends a study without prior agreement of Amgen, the investigator should inform the site personnel. The investigator/site personnel should promptly inform Amgen and the IRB. The investigator/site personnel should also provide Amgen and the IRB 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 Amgen. However, authorized regulatory officials, IRB personnel, Amgen and its 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 Amgen 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 Amgen, by appropriate IRB members, and by inspectors from regulatory authorities.

Identification of subjects and eCRFs shall be by unique subject identification numbers (such as screening or randomization number only). All personal identifiers according to applicable regulations (e.g., name, phone number) must be redacted permanently by the study site personnel and replaced with the subject’s unique identification number in all records and data before transfer to Amgen (or designee).

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

16 References

1. Campochiaro PA. Ocular neovascularization. J Mol Med (Berl). 2013;91(3):311-21.
2. Ho VY, Yeh S, Olsen TW, Bergstrom CS, Yan J, Cribbs BE, et al. Short-term outcomes of aflibercept for neovascular age-related macular degeneration in eyes previously treated with other vascular endothelial growth factor inhibitors. Am J Ophthalmol. 2013;156(1):23-8 e2.
3. Nishikawa K, Oishi A, Hata M, Miyake M, Ooto S, Yamashiro K, et al. Four-Year Outcome of Aflibercept for Neovascular Age-Related Macular Degeneration and polypoidal choroidal vasculopathy. Scientific reports. 2019;9(1):3620.
4. Eylea®. United States Prescribing Information. August 2022.
5. Eylea®. Summary of Product Characteristics. March 2022.

17 Appendices

17.1 Appendix I - Study Administrative Structure

Sponsor:	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320-1799 Phone: +1 (805) 447-1000
Sponsor's Medical Expert:	[redacted], MD, PhD Executive Medical Director Amgen Inc. Phone: [redacted]
Sponsor's Project Manager:	[redacted] Senior Manager, Study Management Amgen Inc. Phone: [redacted]
Medical Monitor:	[redacted] Safety Lead Amgen Inc. Phone: [redacted]
CRO:	ICON Clinical Research South County Dublin Business Park, Leopardstown, Dublin 18, D18X5R3 Ireland Phone: +353-1-2912000 Fax: +353-1-2476260
ABP 938 Manufacturer:	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320-1799 Phone: +1 (805) 447-1000
ABP 938 Distributor:	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320-1799 Phone: +1 (805) 447-1000

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 sites will be maintained.

17.2 Appendix II - Clinical Laboratory Tests

A urine pregnancy test will be performed for female subjects of childbearing potential at a local laboratory at the screening visit.

17.3 Appendix III - Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for male and female subjects of childbearing potential are outlined in Section 4.2.

Male and female subjects of child bearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant or father a child during the study.

Definition of Females of Childbearing Potential

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

Females In The Following Categories Are Not Considered Females Of Childbearing Potential:

- Premenopausal female with one of the following criteria met:
  - Documented hysterectomy.
  - Documented bilateral salpingectomy.
  - 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.
- Post-menopausal female as defined in the following:
  - A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal 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 non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrollment.

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

Note: Failure rate of < 1% per year when used consistently and correctly.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal).
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable).
- Intrauterine device.
- Intrauterine hormonal-releasing system.
- Bilateral tubal ligation/occlusion.
- Vasectomized partner (provided that the 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).

or

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 the 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 the IP; 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 while on-study and for 3 months after IP administration.

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).

Note: If the male's sole female partner is of non-childbearing 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, post-ovulation methods).
- Withdrawal (coitus interruptus).
- Spermicides only.
- Lactational amenorrhea method.

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- The investigator will collect pregnancy information on any female subject who becomes pregnant during the study until the end of study visit.
- Information will be collected 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 in the study. 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 AE or SAE, 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 AE or SAE. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an AE, 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 SAE (e.g., 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 SAE.
- Any SAE occurring as a result of a post-study 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 SAE through spontaneous reporting.

Male Subjects With Partners Who Become Pregnant Or Were Pregnant At The Time Of Enrollment

- In the event a male subject fathers a child during the study, 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 site'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

- The investigator will collect lactation information on any female subject who breastfeeds during the study through end of study visit.
- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen or its designee within 24 hours of the investigator's knowledge of event.

With the female subject's 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 in the study.

AMGEN® Pregnancy Notification Form

Report to Amgen Safety at: US FAX: +1-888-814-8653 or EMAIL: svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: ABP 938 Protocol#: 20210034

Study Design: ☐ **Interventional** ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
ABP 938				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐ N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd___/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

AMGEN Lactation Notification Form

Report to Amgen Safety at: US FAX: +1-888-814-8653 or EMAIL: svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: ABP 938 Protocol#: 20210034

Study Design: ☐ **Interventional** ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):**____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
ABP 938				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____