16.1.1 Study Protocol

The latest version of the protocol used during the study is provided in this section. Previous versions of the protocol are available on request.

Protocol EYP-1901-201 Version 6.0 dated 25-January-2024

EYP-1901
(VOROLANIB INTRAVITREAL INSERT)

PROTOCOL EYP-1901-201 / NCT05381948

A Phase 2, Multicenter, Prospective, Randomized, Double-Masked, Parallel Study of EYP-1901, a Tyrosine Kinase Inhibitor (TKI), Compared to Aflibercept in Subjects with Wet AMD

IND Number	146448
Sponsor:	EyePoint Pharmaceuticals, Inc. 480 Pleasant Street Watertown, MA 02472 USA
Version:	Version 6.0 25 Jan 2024 Version 5.0 21 Dec 2022 Version 4.0 05 Oct 2022 Version 3.0 29 Apr 2022 Version 2.1: 20 Apr 2022 Version 2.0: 12 Apr 2022 Original Protocol: 28 Jan 2022

PROTOCOL APPROVAL PAGE

Protocol Title: **A Phase 2 Multicenter, Prospective, Randomized, Double-Masked, Parallel Study of EYP-1901, a Tyrosine Kinase Inhibitor (TKI), Compared to Aflibercept, in Subjects with Wet AMD**

Protocol Number: **EYP-1901-201**

Version Number: **Version 6.0**

Date: **25 Jan 2024**

This protocol has been reviewed and approved by EyePoint Pharmaceuticals, Inc.

PPD

PPD , MD
PPD
PPD
EyePoint Pharmaceuticals, Inc.

Date

INVESTIGATOR'S AGREEMENT

I have read the attached protocol, concur that it contains all information necessary to conduct the study, and agree to follow the study procedures as outlined in this protocol.

I agree to comply with United States (US) Food and Drug Administration (FDA) regulations (21 CFR Parts 50, 54, 56 and 312) and International Conference on Harmonization (ICH) guidelines. I will not initiate the study until I have obtained written approval by the appropriate Institutional Review Board/Ethics Committee and have complied with all financial and administrative requirements of the governing body of the clinical institution. I will obtain written informed consent from all study participants prior to performing any screening procedures.

This protocol and related information is subject to the Confidentiality Agreement between myself and EyePoint Pharmaceuticals, Inc. and as such must be held in confidence and not disclosed to any third party for a period of seven (7) years from the date of the Confidentiality Agreement, or until said information shall become a matter of public knowledge, or until a formal written agreement for that purpose has been entered into by the parties.

Principal Investigator Signature	Date
Print Name	

PERSONNEL CONTACT INFORMATION

Role in Study	Name	Address and Telephone Numbers
Sponsor	EyePoint Pharmaceuticals, Inc.	EyePoint Pharmaceuticals, Inc. 480 Pleasant Street Watertown, MA 02472 USA Phone: (617) 926-5000 Fax: (617) 926-5050
Principal Investigator	[NEED]	[NEED]
Medical Monitor	PPD , MD	PPD EyePoint Pharmaceuticals, Inc. 480 Pleasant Street, Suite B300 Watertown, MA 02472 USA Cell: PPD
Drug Safety Physician	PPD , MD, MS	Director, Pharmacovigiliance EyePoint Pharmaceuticals, Inc. 480 Pleasant Street, Suite B300 Watertown, MA 02472 USA Cell: PPD email: PPD

SYNOPSIS

Name of Sponsor/Company: EyePoint Pharmaceuticals, Inc. **Name of Investigational Product:** EYP-1901 (Vorolanib intravitreal insert) **Name of Active Ingredient:** Vorolanib	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(for National Authority Use only)*

Title of Study: A Phase 2, Multicenter, Prospective, Randomized, Double-Masked, Parallel Study of EYP-1901, a Tyrosine Kinase Inhibitor (TKI), Compared to Aflibercept, in Subjects with Wet AMD

Protocol Number: EYP-1901-201 **Phase of Development:** 2

Study Sites: Approximately 70 sites in the US

Studied Period: Up to 56 weeks of follow-up

Objectives: To evaluate the efficacy and safety of two doses of the EYP-1901 intravitreal insert in the treatment of subjects with neovascular (wet) age-related macular degeneration (wAMD) compared to aflibercept.

Methodology: A prospective, randomized, double-masked study evaluating ocular efficacy and safety of two doses of the EYP-1901 intravitreal insert compared to aflibercept.

- Previously treated subjects with wAMD who meet the study eligibility criteria will be randomly assigned to treatment with EYP-1901 2,060 µg, EYP-1901 3,090 µg, or aflibercept 2 mg (0.05 mL).
- Sham injections will be used for all treatment arms to maintain masking.
- Subjects in the EYP-1901 arms will receive a dose of aflibercept at Day 1 and Week 4; then at Week 8 subjects will receive a dose of aflibercept and 30 minutes later the assigned EYP-1901 dose. Subjects in the aflibercept arm will receive a dose of aflibercept at Day 1 and Week 4; then at Week 8 they will receive a dose of aflibercept followed by a sham dose 30 minutes later after which they will resume aflibercept dosing at a frequency of every 8 weeks.
- Follow-up examinations will be conducted at Week 12, and every 4 weeks thereafter up to Week 56.

Number of Subjects (planned): Approximately 50 subjects will be enrolled in each of the 3 treatment arms across approximately 70 sites in the US, for a total planned enrollment of 150 subjects.

Inclusion Criteria:

1. Male or female subjects, ≥50 years of age.
2. Documented diagnosis of wAMD in the study eye, with onset of disease that began at any time prior to the Screening Visit.
3. Documented anatomical response (i.e., reduction in fluid on SD-OCT) to previous intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections in the study eye prior to the Screening Visit.
4. Previously treated with at least two anti-VEGF intravitreal injections (i.e., bevacizumab, ranibizumab, aflibercept, or faricimab) for wAMD per standard of care in the study eye within 6 months prior to the Screening Visit.
5. Received previous anti-VEGF therapy 2 to 5 weeks (14 to 35 days) in the study eye prior to the Screening Visit, but no more than 42 days prior to randomization to study treatment on Day 1.

6. Best-corrected visual acuity (BCVA) ETDRS letter score of 35 letters (20/200 Snellen equivalent) to 85 letters (20/20 Snellen equivalent) in the study eye at Screening Visit and on Day 1.
7. Able to understand, and willingness to sign, the informed consent and to provide access to personal health information via Health Insurance Portability and Accountability Act (HIPAA) authorization.
8. Willingness and ability to comply with all scheduled visits, restrictions, and assessments.
9. For women of childbearing potential, or men with female partners of childbearing potential, agreement to the use of an appropriate form of contraception at the Screening Visit and for the duration of the study.

Exclusion Criteria:

All OCT and FA criteria listed below will be confirmed by the Central Reading Center at the Screening Visit.

1. History of pars plana vitrectomy surgery, submacular surgery, or other surgical intervention for AMD in the study eye.
2. Prior treatment with Visudyne® (verteporfin), external beam radiation therapy, or transpupillary thermotherapy in the study eye.
3. Previous treatment with intravitreal corticosteroid injection or device implantation in the study eye.
4. Previous focal laser photocoagulation used for AMD treatment in the study eye.
5. Total choroidal neovascularization (CNV) lesion size >12 disc areas (30.5 mm^2) as assessed by FA in the study eye at Screening Visit.
6. Central subfield thickness (CST) > 350 µm, in the study eye at Screening Visit or Day 1.
7. Intraretinal cystic fluid >25 µm in diameter involving the central subfield and/or disruption of normal morphology (loss of foveal depression, disruption of external limiting membrane) secondary to cystic intraretinal fluid within the central subfield, in the study eye at Screening Visit. Diffuse (non-cystic) intraretinal fluid would not be excluded.
8. Subretinal hemorrhage in the subfoveal/juxtafoveal location and hemorrhage greater than 1 disc area (1.8 mm^2) if located less than 200 µm from the foveal center in the study eye at either Screening Visit or Day 1.
9. Subfoveal fibrosis, atrophy, or scarring in the center subfield in the study eye at Screening Visit.
10. Fibrosis >50% of the total lesion, in the study eye at Screening Visit.
11. Retinal pigment epithelium detachment (RPED) thickness >400 µm at any point within 3 mm of the foveal center in the study eye at either the Screening Visit or Day 1.
12. Retinal pigment epithelial tear in the study eye at Screening Visit or Day 1.
13. Any concurrent intraocular condition in the study eye (e.g., cataract or glaucoma) that, in the opinion of the Investigator, would either require surgical intervention during the study to prevent or treat visual loss that might result from that condition or affect interpretation of the study results.
14. Historical or active intraocular inflammation (grade trace or above) in the study eye, other than expected findings from routine cataract surgery.
15. History of vitreous hemorrhage in the study eye within 12 weeks prior to the Screening Visit.
16. History of rhegmatogenous retinal detachment or treatment for retinal detachment or macular hole (stage 3 or 4) in the study eye.
17. Aphakia or pseudophakia with the absence of the posterior capsule in the study eye (YAG capsulotomy is permitted).

18. Spherical equivalent of the refractive error in the study eye demonstrating >8 diopters of myopia.
19. For subjects who have undergone prior refractive or cataract surgery in the study eye, preoperative refractive error in the study eye exceeding 8 diopters of myopia.
20. Intraocular surgery (including cataract surgery) in the study eye within 12 weeks prior to the Screening Visit.
21. Uncontrolled ocular hypertension or glaucoma in the study eye (defined as intraocular pressure [IOP] >25 mmHg or a cup to disc ratio ≥0.8, despite treatment with 2 or more classes of antiglaucoma medication) and any such condition which the Investigator feels may require a glaucoma-filtering surgery while in the study.
22. History of glaucoma-filtering surgery, tube shunts, or microinvasive glaucoma surgery in the study eye.
23. History of corneal transplant in the study eye.
24. BCVA using ETDRS charts <30 letters (20/250 Snellen equivalent) in the fellow eye.
25. Worsening of BCVA ≥10 ETDRS letters in the study eye from Screening Visit to Day 1.
26. Presence of CNV in either eye due to other causes aside from wAMD, at Screening Visit.
27. Treatment with Visudyne® in the fellow eye <7 days prior to the Screening Visit.
28. Prior participation in a clinical trial involving investigational anti-angiogenic drugs administered in either eye or systemically within 8 weeks prior to the Screening Visit.
29. Prior participation in a clinical trial involving investigational ocular gene therapy trial for either eye.
30. History of idiopathic or autoimmune-associated uveitis in either eye.
31. Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.
32. Presence of any other systemic or ocular condition which, in the judgment of the investigator, could make the subject inappropriate for entry into this study.
33. Uncontrolled blood pressure (defined as systolic >180 mmHg and/or diastolic >100 mmHg), based on the average of three readings taken with the subject in a resting state.
34. Myocardial infarction within 6 months prior to screening or New York Hospital Association (NYHA) Class III or IV heart failure, uncontrolled atrial fibrillation, uncontrolled angina, cardiomyopathy, ventricular arrhythmias or other cardiac conditions which, in the judgment of the investigator, could make the subject inappropriate for entry into this study.
35. Serious non-healing wound, ulcer, or bone fracture.
36. HbA1c greater than 7% at the Screening Visit.
37. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of EYP-1901.
38. Current treatment for any active systemic infection.
39. Previous use of any systemic anti-VEGF agents or intraocular brolucizumab in the study eye.
40. Use of oral corticosteroids (prednisone >10 mg/day or equivalent) within 30 days prior to the Screening Visit.
41. History or presence of bleeding disorders, including platelet disorders, hemorrhage, acquired or hereditary coagulation disorders (including deep vein thrombosis and pulmonary embolisms), acquired or hereditary vascular disorders, stroke, or transient ischemic attack.
42. Excluding certain skin cancers (specifically, basal cell carcinoma and squamous cell carcinoma), any malignancy receiving treatment, or in remission less than 5 years prior to study entry.
43. History of allergy to fluorescein, not amenable to treatment.

44. Inability to obtain fundus photographs, fluorescein angiography (FA), fundus autofluorescence, or spectral-domain – optical coherence tomography (SD-OCT) images of sufficient quality to be analyzed and graded by the central reading center.
45. Historical or active diagnosis of any medical or psychological condition that could interfere with the ability of the subject to give informed consent, or to comply with study or follow-up procedures.
46. Previous participation in any ocular or non-ocular (systemic) disease studies of investigational drugs within 30 days prior to the Screening Visit (excluding vitamins and minerals).
47. Use of anti-mitotic or anti-metabolite therapy within 30 days or 5 elimination half-lives of the Screening Visit, whichever is longer.
48. Intolerance, contraindication, or hypersensitivity to topical anesthetics, dyes, povidone iodine, mydriatic medications, or any of the ingredients of the EYP-1901 insert.
49. Requirement for continuous use of any protocol-prohibited medications or treatments.
50. Pregnant or nursing females; females of childbearing potential who are unwilling to use an acceptable method of contraception during the study as outlined in this protocol.

Treatment Assignment: Subjects will receive intravitreal aflibercept 2 mg (0.05 mL) on Day 1 and at Week 4. At Week 8, subjects will receive aflibercept and 30 minutes (+/- 10 minutes) later will receive either 2,060 µg or 3,090 µg of the EYP-1901 intravitreal insert (the test article) in the designated study eye.

Control: Subjects will receive intravitreal aflibercept 2 mg (0.05 mL) dose on Day 1 and at Week 4. At Week 8, subjects will receive aflibercept and 30 minutes (+/- 10 minutes) later will receive a sham injection, and resume aflibercept dosing at a frequency of every 8 weeks (or when predefined re-treatment criteria are met) thereafter as the control treatment.

Duration of Treatment: Duration of release of the EYP-1901 active ingredient (vorolanib) is expected to be at least 9 months.

Test Article Therapy: Each EYP-1901 intravitreal, bioerodible insert is 8 mm long and is designed to deliver vorolanib into the vitreous humor for at least 9 months. Multiple inserts will be administered to the study eye at Week 8 by injection through the pars plana using a pre-loaded applicator with a 22-gauge needle as follows:

- 2,060 µg dose; 2 inserts, 22-gauge needle
- 3,090 µg dose; 3 inserts, 22-gauge needle

Designation of Study Eye: For subjects with unilateral wAMD, the affected eye will be designated as the study eye; for subjects with bilateral wAMD, the study eye will be the more severely affected eye meeting the inclusion/exclusion criteria (i.e., the eye having the worse BCVA or if equal, the eye clinically judged to be the more severely affected eye as determined by the Investigator). If the eyes are symmetrically affected, the study eye will be the right eye.

Study Procedures: Assessments will include BCVA by Early Treatment Diabetic Retinopathy Study (ETDRS), anterior/posterior segment ocular examination, IOP, FA, color fundus photography (CFP), SD-OCT, SD-OCT angiography (SD-OCTA) at pre-specified study sites where equipment is available, vital sign measurements, ECG, treatment-emergent ocular and non-ocular adverse events (TEAEs), clinical laboratory evaluations (hematology, serum chemistry, coagulation, and urinalysis), bioanalytical testing of plasma and aqueous humor vorolanib and its main metabolite levels (see details in Table 5–1). During unscheduled visit or if posterior inflammation is present in study eye, CFP and OCT of study eye should be collected at a minimum.

In the event the subject requires vitrectomy during the study, the unmasked investigator or designee will collect a vitreous sample and EYP-1901 implants (if applicable) to be sent to the Sponsor as described in Appendix 3.

Follow-up Visits: Following Day 1, follow up examinations will be conducted at Week 4, 8, 12 and every 4 weeks thereafter up to Week 56 (see details in Table 5–1).

Rescue Criteria in the Study Eye:

Starting from Week 12, aflibercept may be administered in the study eye at the Investigator's discretion if at least one of the following criteria is met:

- BCVA reduction of ≥5 letters from best on study measurement due to wAMD
  AND
  Increase in CST of ≥75 microns on SD-OCT from lowest on study measurement
- BCVA reduction of ≥10 letters from best on study measurement due to wAMD
- Increase in CST of ≥100 microns on SD-OCT from lowest on study measurement from two consecutive visits
- Presence of new or worsening vision-threatening hemorrhage due to wAMD

If the above rescue criteria are not met, the Investigator may still determine the need for administering a rescue medication in the best interest of the subject's welfare. In this case the Investigator is required to contact the Medical Monitor prior to rescue if feasible.

Masking: Except for the investigators administering the study treatments, masking will be maintained for both subjects and the investigators conducting the study assessments. Sham injections will be used during the study in all treatment arms to maintain masking of the study treatments. Only the Sponsor/CRO will be unmasked at Week 32 to conduct endpoint analysis.

Criteria for Evaluation:

Primary Endpoint:

- Average change in BCVA from Day 1 averaged over Week 28 and Week 32.

Secondary Endpoints:

- Change from Day 1 in BCVA up to Week 56
- Proportion of subjects with ≥5, ≥10, and ≥15 BCVA letters changes from Day 1 up to Week 56
- Proportion of subjects not receiving a rescue injection of aflibercept in the study eye up to Week 56
- Median time to first rescue aflibercept injection in the study eye following the EYP-1901 dose at Week 8
- Number of aflibercept injections by Week 56
- Mean change from Day 1 in CST in microns by SD-OCT up to Week 56
- Change from Day 1 in height of subretinal fluid by SD-OCT up to Week 56
- Change from Day 1 in proportion of subjects with no detectable intraretinal fluid/cysts in the central subfield up to Week 56
- Change from Day 1 in total lesion area by FA up to Week 56
- Change from Day 1 in total CNV area by FA up to Week 56
- Systemic exposure to EYP-1901 measured through plasma levels up to Week 56
- Ocular exposure to EYP-1901 measured through aqueous levels up to Week 32
- Rates of ocular (study eye and fellow eye) and non-ocular TEAEs up to Week 56

Statistical Methods:

Sample Size:

The primary objective of the study is to provide efficacy and safety data in a prospective, randomized, double-masked, controlled trial. The study will be unmasked upon completion of Week 32, at which point efficacy and safety endpoints will be analyzed for all randomized subjects. CCI [redacted]

Approximately 150 subjects will be randomized at 1:1:1 ratio to each of three treatment arms.

Efficacy and Safety Analyses:

Descriptive statistics by treatment arm will be provided for all TEAEs, BCVA and imaging endpoints, along with plasma and aqueous humor pharmacokinetic data. Frequency counts and percentage of subjects will be provided by MedDRA system organ class (SOC) and preferred term (PT) by treatment arm. Concomitant medications will be presented after coding with WHO-Drug Dictionary terms. Clinical laboratory assessments will be presented using descriptive statistics by treatment arm.

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List of Abbreviations

Table 1–1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AMD	Age-related macular degeneration
ATC	Anatomical Therapeutic Chemical
BCVA	Best corrected visual acuity
CFP	Color fundus photography
CFR	(US) Code of Federal Regulations
CI	Confidence interval
CNV	Choroidal neovascularization
CPR	Cardiopulmonary resuscitation
CRA	Clinical Research Associate
CRO	Contract Research Organization
CST	Central subfield retinal thickness
CTCAE	(National Cancer Institute's) Common Toxicity Criteria for Adverse Events
DME	Diabetic macular edema
EC	Ethics Committee
eCRF	Electronic case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
FDA	Food and Drug Administration
GCP	Good Clinical Practice (guidelines)
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug application
IOP	Intraocular pressure
IRB	Institutional Review Board
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
NYHA	New York Hospital Association
OTC	Over-the-counter
OU	Both eyes
PDGF	Platelet-derived growth factor
PK	Pharmacokinetic
RPED	Retinal pigment epithelium detachment
PRN	As needed
PT	Preferred term
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD-OCT	Spectral-domain – optical coherence tomography
SD-OCTA	Spectral-domain – optical coherence tomography angiography
SE	Study eye
SOC	System Organ Class
SOP	Standard Operating Procedure
SS-OCTA	Swept-source – optical coherence tomography angiography
SUSAR	Suspected, unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
US/USA	United States of America
VEGF	Vascular endothelial growth factor
wAMD	Wet age-related macular degeneration
WHO	World Health Organization

1 INTRODUCTION

1.1 Background

Vorolanib is a multi-kinase inhibitor of both vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), which is structurally related to other multi-kinase inhibitors and is a potent inhibitor of angiogenesis. This drug was originally developed as an oral pharmaceutical formulation to treat patients with pathologic angiogenesis found in certain solid tumors, in von Hippel-Lindau disease, and in exudative age-related macular degeneration (AMD). As a small molecule, vorolanib has more recently been developed as an intravitreal formulation utilizing Durasert®, a proprietary sustained delivery technology used in FDA approved intraocular products indicated for the treatment of posterior segment uveitis. Examples include Retisert® (Bausch & Lomb, Inc., USA) and Yutiq® (Alimera Sciences, USA), and for the treatment of diabetic macular edema (DME), such as Iluvien® (Alimera Sciences, USA). EYP-1901 intravitreal insert is a bioerodible, sterile, sustained-release drug delivery system formulated in Durasert® and designed to release microgram levels of vorolanib into the ocular vitreous chamber for the treatment of wet age-related macular degeneration (wAMD).

1.2 Overview of wAMD

AMD is one of the most common causes of visual loss, projected to affect nearly 200 million people worldwide (Wong et al. 2014). Late-stage AMD, characterized by macular atrophy (known as geographic atrophy) and choroidal neovascularization (CNV), affects nearly 11 million people (Wong et al. 2014). Roughly two-thirds of the cases of late-stage AMD involve CNV, manifested by the exudation of fluid and blood, often resulting in vision loss and a fibrotic scar if untreated. Intravitreal injections of VEGF inhibitors diminish the extent of exudation arising from CNV. Ranibizumab (Genentech, USA), bevacizumab (Genentech, USA) and aflibercept (Regeneron Pharmaceuticals, USA) inhibit multiple isoforms of VEGF-A and are used worldwide to treat CNV secondary to AMD.

The suggestion that VEGF might be driving the CNV and associated edema seen in AMD led to a paradigm shift with the success of the first anti-VEGF therapy, pegaptanib sodium (Ferrara 2009; Yancopoulos 2010). Monthly intravitreal injections of 0.5 mg ranibizumab, a humanized monoclonal antibody fragment that blocks VEGF, not only prevent vision loss in most patients but also lead to significant visual gain in approximately one third of patients (Rosenfeld et al. 2006; Brown et al. 2006). The risk of rare but serious adverse events resulting from the intravitreal procedure, together with the significant burden of making monthly visits to their retinal specialist, have led to extensive efforts to decrease injection and monitoring frequency. However, fixed quarterly (Regillo et al. 2008; Schmidt-Erfurth et al. 2011) or “as needed” (PRN) dosing regimens (Boyer et al. 2009; Singer et al. 2012), without requiring monthly monitoring visits, were not effective at maintaining vision.

Intravitreal aflibercept, a soluble decoy receptor fusion protein, dosed monthly or every 2 months after 3 initial monthly doses produced similar efficacy and safety outcomes as monthly ranibizumab (Heier et al. 2012). This study demonstrated that aflibercept was an effective treatment for AMD, with the every-2-month regimen offering the potential to reduce the risk from monthly intravitreal injections and the burden of monthly monitoring.

1.3 Study Rationale

Despite the introduction of a number of improved anti-VEGF biologic agents in recent years, there remains a need for new therapies that will provide equivalent efficacy and anatomic disease control while reducing the need for frequent injections and the burden of mandatory monthly monitoring visits. EyePoint Pharmaceuticals, the Sponsor of this study, has developed EYP-1901 intravitreal insert, a sustained and controlled delivery formulation of vorolanib over a period of at least 9 months as a therapy to address this unmet medical need.

1.4 Nonclinical Experience with EYP-1901

X-82, an oral vorolanib formulation, and EYP-1901(Vorolanib intravitreal insert) were investigated in nonclinical efficacy models and in safety and pharmacokinetic nonclinical models. For a summary of the nonclinical experience with these drug formulations please refer to the current EYP-1901 Investigator's Brochure (IB).

1.5 Clinical Experience with EYP-1901

This is the second clinical investigational study of EYP-1901 (Vorolanib intravitreal insert); a previous phase 1 dose escalation trial in patients with wet AMD was initiated in January 2021 (first patient dosed). Interim safety and efficacy analyses conducted upon completion of Week 24 provided support for initiation of the present Ph 2 study. For X-82 (oral vorolanib), two previous studies were conducted in wAMD (Jackson et al. 2017; Cohen et al. 2020). For additional details on the clinical experience from previous EYP-1901 and X-82 studies please refer to the current EYP-1901 IB.

1.6 Clinical Experience with Aflibercept

Two randomized clinical trials were conducted to establish the safety and efficacy in 2412 patients with wAMD (Heier et al. 2012; Schmidt-Erfurth et al. 2014). FDA approval was granted in 2011 for aflibercept under the brand name EYLEA® for the treatment of wAMD. Consult the EYLEA® (aflibercept) label for additional information.

2 STUDY OBJECTIVES

The primary objective is to evaluate the efficacy of two doses (2,060 µg and 3,090 µg) of the EYP-1901 intravitreal insert on visual acuity compared to aflibercept. The primary endpoint is average change in best corrected visual acuity (BCVA) from Day 1 averaged over Week 28 and Week 32.

The secondary objectives are to evaluate the use of rescue treatments in the study eye, the retinal functional and anatomical response to treatment, and the safety following treatment with EYP-1901 intravitreal insert compared to aflibercept. The secondary objectives will be assessed with the following secondary endpoints:

- Change from Day 1 in BCVA up to Week 56
- Proportion of subjects with ≥5, ≥10, and ≥15 BCVA letters changes from Day 1 up to Week 56

- Proportion of subjects not receiving a rescue injection of aflibercept in the study eye up to Week 56
- Median time to first rescue aflibercept injection in the study eye following the EYP-1901 dose at Week 8
- Number of aflibercept injections by Week 56
- Mean change from Day 1 in CST in microns by SD-OCT up to Week 56
- Change from Day 1 in height of subretinal fluid by SD-OCT up to Week 56
- Change from Day 1 in proportion of subjects with no detectable intraretinal fluid/cysts in the central subfield up to Week 56
- Change from Day 1 in total lesion area by FA up to Week 56
- Change from Day 1 in total CNV area by FA up to Week 56
- Systemic exposure to EYP-1901 measured through plasma levels up to Week 56
- Ocular exposure to EYP-1901 measured through aqueous levels up to Week 32
- Rates of ocular (study eye and fellow eye) and non-ocular TEAEs up to Week 56

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

The design for this study is a prospective, randomized, double-masked, multicenter trial comparing two different doses of the EYP-1901 intravitreal insert to aflibercept in previously-treated subjects (≥50 years of age) with wAMD. Up to 150 subjects will be randomized on a 1:1:1 basis to the 3 different treatment arms (2,060 µg EYP-1901, 3,090 µg EYP-1901, or 2 mg [0.05 mL] aflibercept) across approximately 70 sites, such that each arm will include up to 50 subjects. All subjects, irrespective of treatment arm, will receive a dose of aflibercept on Day 1 and Week 4 in the designated study eye. At Week 8, all subjects will receive a third aflibercept injection and subjects in the EYP-1901 treatment arms will receive the assigned dose of the EYP 1901 intravitreal insert 30 minutes (+/- 10 minutes) following aflibercept injection, which is expected to deliver vorolanib into the vitreous humor for at least 9 months, while subjects in the aflibercept treatment arm will receive a sham injection 30 minutes (+/- 10 minutes) later to maintain masking. Subjects in the aflibercept arm will be re-treated with aflibercept at Week 16 and every 8 weeks thereafter, or when pre-defined re-treatment criteria are met (see details in Section 6.6.4 Rescue Treatment), while subjects in the EYP-1901 treatment arms will receive a sham injection (or aflibercept when the pre-defined re-treatment criteria are met) during these visits. Subjects will be followed for up to 56 weeks from the first dosing at the Baseline Visit (Day 1). The primary objective of this study is to evaluate the efficacy and safety of one dose, two different concentrations of the EYP-1901 intravitreal insert in the treatment of subjects with wAMD compared to aflibercept.

3.1.1 General Study Methods

For subjects with unilateral wAMD, the affected eye will be designated as the study eye; for subjects with bilateral wAMD, the study eye will be the more severely affected eye meeting the

inclusion/exclusion criteria (i.e., the eye having the worse BCVA or if equal, the eye clinically judged to be the more severely affected eye as determined by the Investigator). If the eyes are symmetrically affected, the study eye will be the right eye.

Subjects aged 50 years or greater with an active diagnosis of wAMD at screening, BCVA in the study eye using ETDRS charts of 35 letters (20/200 Snellen equivalent) to 85 letters (20/20 Snellen equivalent), and who satisfy all other protocol eligibility criteria up until dosing on Day 1, will be enrolled and receive the assigned study treatment.

Monthly follow-up examinations will be conducted through the 56 weeks following dosing on Day 1. The schedule of study procedures and assessments is presented in Table 5–1. Study procedures will include: BCVA by ETDRS, anterior/posterior segment ocular examination, IOP, FA, color fundus photography (CFP), SD-OCT, SD-OCTA at pre-specified study sites where equipment is available, vital signs measurements, ECG, ocular and non-ocular TEAEs, clinical laboratory evaluations (hematology, serum chemistry, coagulation, and urinalysis), bioanalytical testing of plasma and aqueous humor vorolanib and its main metabolite levels. During an unscheduled visit or if posterior inflammation is present in the study eye, CFP and OCT of the study eye should be collected at a minimum.

In the event the subjects require vitrectomy during the study, the unmasked investigator or designee will collect a vitreous sample and EYP-1901 implants (if applicable) to be sent to the Sponsor as described in Appendix 3.

3.2 Masking and Randomization

Except for the investigators administering the study treatments, masking will be maintained for both subjects and the investigators conducting the study assessments. Sham injections will be used during the study to maintain masking of the study treatments. Only the Sponsor /CRO will be unmasked at Week 32 to conduct endpoint analysis.

The randomization code will be generated with a computer program according to the study design, the number of subjects and the number of treatments. The random allocation of each treatment to each subject will be done in such a way that the study is balanced. Randomization will occur on Day 1.

3.3 Discussion of Study Design, Including the Choice of Control Groups

The prospective, randomized, double-masked study with an active control group is an acceptable design for the evaluation of comparative efficacy and safety of the intravitreal products EYP-1901 and aflibercept.

The two doses (2,060 µg or 3,090 µg) chosen for EYP-1901 were based on the safety profile through Week 24 in the completed Phase 1 DAVIO study (see details in Section 1.5).

The 2 mg (0.05 mL) dose chosen for aflibercept was based on the dosage and administration recommendations for wAMD provided in the EYLEA® (aflibercept) label.

3.4 Duration of Study

Total study participation will be approximately 59 weeks (including the Screening period). The initial Screening Visit is from Days -21 to -7, during which time subjects may be enrolled, and then the study treatments/control will be administered starting on Day 1 if the eligibility criteria

are still met. Subjects who require a longer period between initial screening and Day 1 will be re-screened prior to entry into the study. After dosing of study treatments through Week 8, the follow-up period will be up to 48 weeks, specifically visits at Week 12 and every 4 weeks thereafter. Sham injections will be given when necessary to maintain masking. The primary efficacy endpoint will be evaluated at Weeks 28 and 32. Eligible subjects who are enrolled in this study will be seen for the scheduled study visits over approximately 14 months depending on the time between Day 1 and the final study visit. Screen failures will be recorded along with the reason(s) for not meeting the eligibility criteria. Study completion is achieved at the Week 56 visit (End of Study Visit).

3.5 Recording of Injection Procedure

The injection procedure of EYP-1901 or aflibercept may be photographed or video-recorded according to the site's standard procedures. Images and/or video will be provided to the Sponsor who may distribute them to other participating sites or other appropriate parties. Subject-identifying information must be redacted from all images and video prior to distribution.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

Three treatment groups of up to 50 subjects each will be enrolled to assess the efficacy and safety of 2,060 µg or 3,090 µg EYP-1901 intravitreal insert compared to aflibercept 2 mg (0.05 mL) injections.

Subjects will be enrolled in the study only if they meet all the following eligibility criteria during the Screening period and with confirmed eligibility at treatment randomization on Day 1, with the exception of criteria requiring confirmation by central reading center, which will be assessed at screening only. The Investigator will exercise medical and scientific judgement in deciding whether a laboratory finding, or other assessment should be reassessed within the Screening period. Subjects that do not meet all the requirements as outlined in the eligibility criteria (screen failures), may be rescreened at the discretion of the Investigator.

4.1 Inclusion Criteria

Subjects will be considered eligible for participation in the study if all of the following inclusion criteria are satisfied:

1. Male or female subjects, ≥50 years of age.
2. Documented diagnosis of wAMD in the study eye, with onset of disease that began at any time prior to the Screening Visit.
3. Documented anatomical response (i.e., reduction in fluid on SD-OCT) to previous intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections in the study eye prior to the Screening Visit.
4. Previously treated with at least two anti-VEGF intravitreal injections (i.e., bevacizumab, ranibizumab, aflibercept, or faricimab) for wAMD per standard of care in the study eye within 6 months prior to the Screening Visit.
5. Received previous anti-VEGF therapy 2 to 5 weeks (14 to 35 days) in the study eye prior to Screening Visit, but no more than 42 days prior to randomization to study treatment on Day 1.

6. BCVA ETDRS letter score of 35 letters (20/200 Snellen equivalent) to 85 letters (20/20 Snellen equivalent) in the study eye at the Screening Visit and on Day 1.
7. Able to understand, and willingness to sign, the informed consent and to provide access to personal health information via Health Insurance Portability and Accountability Act (HIPAA) authorization.
8. Willingness and ability to comply with all scheduled visits, restrictions, and assessments.
9. For women of childbearing potential, or men with female partners of childbearing potential, agreement to the use of an appropriate form of contraception at the Screening Visit and for the duration of the study.

4.2 Exclusion Criteria

All OCT and FA criteria listed below will be confirmed by the Central Reading Center at the Screening Visit:

1. History of pars plana vitrectomy surgery, submacular surgery, or other surgical intervention for AMD in the study eye.
2. Prior treatment with Visudyne® (verteporfin), external beam radiation therapy, or transpupillary thermotherapy in the study eye.
3. Previous treatment with intravitreal corticosteroid injection or device implantation in the study eye.
4. Previous focal laser photocoagulation used for AMD treatment in the study eye.
5. Total CNV lesion size >12 disc areas (30.5 mm^2) as assessed by FA in the study eye at the Screening Visit.
6. Central subfield thickness (CST) > 350 µm in the study eye at the Screening Visit or Day 1.
7. Intraretinal cystic fluid >25 µm in diameter involving the central subfield and/or disruption of normal morphology (loss of foveal depression, disruption of external limiting membrane) secondary to cystic intraretinal fluid within the central subfield, in the study eye at Screening Visit. Diffuse (non-cystic) intraretinal fluid would not be excluded.
8. Subretinal hemorrhage in the subfoveal/juxtafoveal location and hemorrhage greater than 1 disc are (1.8 mm^2) if located less than 200 µm from the foveal center in the study eye at either the Screening Visit or Day 1.
9. Subfoveal fibrosis, atrophy, or scarring in the center subfield in the study eye at the Screening Visit
10. Fibrosis >50% of the total lesion, in the study eye at the Screening Visit.
11. Retinal pigment epithelium detachment (RPED) thickness >400 µm at any point within 3 mm of the foveal center in the study eye at either the Screening Visit or Day 1.
12. Retinal pigment epithelial tear in the study eye at the Screening Visit or Day 1.

13. Any concurrent intraocular condition in the study eye (e.g., cataract or glaucoma) that, in the opinion of the Investigator, would either require surgical intervention during the study to prevent or treat visual loss that might result from that condition or affect interpretation of the study results.
14. Historical or active intraocular inflammation (grade trace or above) in the study eye, other than expected findings from routine cataract surgery.
15. History of vitreous hemorrhage in the study eye within 12 weeks prior to the Screening Visit.
16. History of rhegmatogenous retinal detachment or treatment for retinal detachment or macular hole (stage 3 or 4) in the study eye.
17. Aphakia or pseudophakia with the absence of the posterior capsule in the study eye (YAG capsulotomy is permitted).
18. Spherical equivalent of the refractive error in the study eye demonstrating >8 diopters of myopia.
19. For subjects who have undergone prior refractive or cataract surgery in the study eye, preoperative refractive error in the study eye exceeding 8 diopters of myopia.
20. Intraocular surgery (including cataract surgery) in the study eye within 12 weeks prior to the Screening Visit.
21. Uncontrolled ocular hypertension or glaucoma in the study eye (defined as intraocular pressure [IOP] >25 mmHg or a cup to disc ratio ≥0.8, despite treatment with 2 or more classes of antiglaucoma medication) and any such condition which the Investigator feels may require a glaucoma-filtering surgery while in the study.
22. History of glaucoma-filtering surgery, tube shunts, or microinvasive glaucoma surgery in the study eye.
23. History of corneal transplant in the study eye.
24. BCVA using ETDRS charts <30 letters (20/250 Snellen equivalent) in the fellow eye.
25. Worsening of BCVA ≥ 10 ETDRS letters in the study eye from the Screening Visit to Day 1.
26. Presence of CNV in either eye due to other causes aside from wAMD at the Screening Visit.
27. Treatment with Visudyne® in the fellow eye <7 days prior to the Screening Visit.
28. Prior participation in a clinical trial involving investigational anti-angiogenic drugs administered in either eye or systemically within 8 weeks prior to the Screening Visit.
29. Prior participation in a clinical trial involving investigational ocular gene therapy trial for either eye.
30. History of idiopathic or autoimmune-associated uveitis in either eye.
31. Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.

32. Presence of any other systemic or ocular condition which, in the judgment of the investigator, could make the subject inappropriate for entry into this study.
33. Uncontrolled blood pressure (defined as systolic >180 mmHg and/or diastolic >100 mmHg), based on the average of three readings taken with the subject in a resting state.
34. Myocardial infarction within 6 months prior to screening or New York Hospital Association (NYHA) Class III or IV heart failure, uncontrolled atrial fibrillation, uncontrolled angina, cardiomyopathy, ventricular arrhythmias or other cardiac conditions which, in the judgment of the investigator, could make the subject inappropriate for entry into this study.
35. Serious non-healing wound, ulcer, or bone fracture.
36. HbA1c greater than 7% at the Screening Visit.
37. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of EYP-1901.
38. Current treatment for any active systemic infection.
39. Previous use of any systemic anti-VEGF agents or intraocular brolucizumab in the study eye.
40. Use of oral corticosteroids (prednisone >10 mg/day or equivalent) within 30 days prior to the Screening Visit.
41. History or presence of bleeding disorders, including platelet disorders, hemorrhage, acquired or hereditary coagulation disorders (including deep vein thrombosis and pulmonary embolisms), acquired or hereditary vascular disorders, stroke, or transient ischemic attack.
42. Excluding certain skin cancers (specifically, basal cell carcinoma and squamous cell carcinoma), any malignancy receiving treatment, or in remission less than 5 years prior to study entry.
43. History of allergy to fluorescein, not amenable to treatment.
44. Inability to obtain fundus photographs, FA, fundus autofluorescence, or SD-OCT images of sufficient quality to be analyzed and graded by the central reading center.
45. Historical or active diagnosis of any medical or psychological condition that could interfere with the ability of the subject to give informed consent, or to comply with study or follow-up procedures.
46. Previous participation in any ocular or non-ocular (systemic) disease studies of investigational drugs within 30 days prior to the Screening Visit (excluding vitamins and minerals).
47. Use of anti-mitotic or anti-metabolite therapy within 30 days or 5 elimination half-lives of the Screening Visit, whichever is longer.
48. Intolerance, contraindication or hypersensitivity to topical anesthetics, dyes, povidone iodine, mydriatic medications, or any of the ingredients of the EYP-1901 insert.

49. Requirement for continuous use of any protocol-prohibited medications or treatments.
50. Pregnant or nursing females; females of childbearing potential who are unwilling or unable to use an acceptable method of contraception during the study as outlined in this protocol.

4.3 Pregnancy and Contraception

Women of childbearing potential are advised to use effective method of birth control before the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of aflibercept. Examples of acceptable, effective methods of birth control are: oral contraceptive pill (e.g., Ortho Tri-Cyclen®); injection (e.g., Depo Provera®); implant (e.g., Norplant®); patch (e.g., Ortho Evra Patch®); vaginal ring (e.g., NuvaRing®); intrauterine coil (e.g., Mirena® coil); intrauterine device (IUD) with or without hormones; or a barrier method (e.g., latex condom, diaphragm, or cap) used **with an additional form of contraception** (i.e., **two methods** [e.g., sponge, spermicide, hormonal contraceptive pill, or injection]). A female is considered to be of childbearing potential UNLESS she is post-menopausal (no menses for two consecutive years) or without a uterus and/or both ovaries.

Before enrolling a woman of childbearing potential, Investigators must review with the subject the following:

- Pregnancy prevention information
- Risks to unborn child(ren)
- Risks if currently nursing
- Any drug interactions with hormonal contraceptives
- Contraceptives in current use; and
- Guidelines for the follow-up of a reported pregnancy

For subjects who become pregnant during the study positive urine pregnancy results will be confirmed by a serum pregnancy test. Based on the anti-VEGF mechanism of action for both EYP-1901 and aflibercept the study treatments may pose a risk to human embryofetal development. Subjects should continue participation in the study at the discretion of the Investigator and only if the potential benefit justifies the potential risk to the fetus. Subjects should be instructed to notify the Investigator if it is determined after completion of the study that they became pregnant while participating in the study. However, it is the Investigator's responsibility to pursue the follow-up. Whenever possible, a pregnancy should be followed to term, any premature terminations of pregnancy should be reported, and the status of the mother and the child should be reported to the Medical Monitor after delivery.

Subjects who are not of childbearing potential meeting one or both of the following criteria will not be required to be tested for pregnancy or use contraception:

- Amenorrheic for >2 years without a hysterectomy and bilateral oophorectomy and a FSH value in the postmenopausal range upon pre-trial (screening) evaluation.
- Post-hysterectomy, bilateral oophorectomy, or tubal ligation. Tubal ligation must be confirmed with medical records of the actual procedure.

4.4 Study Termination Criteria

Each subject will be informed that they are free to withdraw from the study at any time. The Investigator, the Investigator in consultation with the Medical Monitor, or the Medical Monitor may exercise his or her medical judgment to terminate a subject's participation in the study if it is in the best interest of the subject.

If a subject withdraws from the study during the follow-up period, the Investigator should make every effort to have the subject return to the clinic for the end of study safety evaluations.

Medical Monitoring for this study will be conducted by:

PPD , MD
PPD
EyePoint Pharmaceuticals, Inc.
480 Pleasant Street, Suite B300
Watertown, MA 02472 USA
Cell: PPD

The Sponsor reserves the right to terminate the study at any time. Every effort should be made to collect all data required by the protocol during or following the subject's Early Termination Visit.

In cases of early termination, every effort should be made to complete the case report forms and report the results as thoroughly as possible. A termination electronic case report form (eCRF) page should be completed for every subject who received study treatment whether or not the subject completed the study. The reason for any early termination from the study should be indicated on this form. The primary reason for a subject's early termination should be selected from the following standard categories:

Adverse Event (AE): Clinical or laboratory events occurred that in the medical judgment of the Investigator for the best interest of the subject are grounds for discontinuation. This includes serious AEs (SAEs) and non-serious AEs regardless of the relationship to study drugs.

Subjects who are withdrawn due to AEs must be followed until there is either:

a. Resolution
b. Stabilization or severity to the National Cancer Institute's Common Toxicity Criteria for Adverse Events (CTCAE) Grade 1/mild
c. Returned to baseline status
d. Subject is lost to follow-up
e. The event is otherwise explained by the Investigator

Death: The subject died during the study.

Withdrawal of Consent: The subject desired to withdraw from further participation in the study in the absence of a medical need to withdraw as determined by the Investigator. If the subject gave a reason for this desire, this should be recorded.

Major Protocol Violation: There was failure to meet the protocol entry criteria or the subject failed to adhere to the protocol requirements or received prohibited medication (e.g., subject

failure to follow instructions, or inability to complete study assessments). The violation necessitated premature termination from the study.

Other: The subject was terminated for a reason other than those listed above, such as termination of study by the Sponsor or a regulatory authority. The Investigator must specify the reason.

5 STUDY PROCEDURES

To ensure the health of both eyes, observations of both the study eye and non-study (fellow) eye should be made as described in the Schedule of Study Procedures and Assessments (Table 5–1; all bilateral procedures and assessments are indicated by cells shaded gray in Table 5–1).

BCVA by ETDRS: The equipment and procedures necessary for testing BCVA are presented in Appendix 1. Visual acuity is always tested with the subject's best correction and should be measured prior to pupil dilation and slit lamp biomicroscopy examination or any drops or ointments are used. BCVA by ETDRS will be measured at every study visit (Table 5–1). Visual acuity testing in this study is required at a distance of 4 meters, and for subjects with reduced vision at 1 meter. Each site should have at least one certified refractionist available for the use of ETDRS charts. **An ETDRS-certified refractionist** should perform all protocol refraction and BCVA measurements required by the protocol.

Slit lamp Biomicroscopy: Anterior chamber evaluation will be conducted using a slit beam of 1 mm height and 1 mm width with maximum luminance through the highest powered lens using the Investigator's standard slit lamp equipment and procedure. This procedure will be the same for all subjects observed at the Investigator's site. Ocular signs assessments, including vitreous haze, the presence of anterior chamber cells, and will be scored according to the scales and conventions presented in Appendix 2. Ocular examinations will be done at the study visits noted in (Table 5–1).

Dilated Ophthalmoscopy: Will be performed according to the Investigator's preferred procedure. This procedure will be the same for all subjects observed at the Investigator's site (Appendix 2). Ocular examinations will be done at the study visits noted in (Table 5–1).

Intraocular Pressure/Tonometry: IOP will be measured as described in Appendix 2 at the study visits noted in (Table 5–1).

Fluorescein Angiography and Color Fundus Photography: A study-certified photographer will take mydriatic stereoscopic color photographs and a fluorescein angiogram of both eyes according to the standardized procedures described in the Study Manual. Photography must be performed after testing visual acuity if these procedures are performed on the same day. FA/CFP will be done at the study visits noted in (Table 5–1).

SD-OCT and SD-OCTA Assessments: Spectral-domain – optical coherence tomography assessments of both eyes will be taken by a study-certified OCT technician according to the standardized procedures described in the Study Manual. Because the eye must be dilated for OCT, it must be performed after testing visual acuity if these procedures are performed on the same day. SD-OCT and SD-OCTA (at pre-specified study sites where equipment is available) testing will be done at the study visits noted in (Table 5–1). Please note that either SD-OCTA or swept-source – optical coherence tomography angiography (SS-OCTA) imaging could be collected in this study. Additionally, historical OCT images in original format for the 9 months

prior to Screening are to be submitted to the central reading center. In the event that images are not available in the original format of capture, PDFs of the OCTs may be submitted.

Ocular and Non-ocular TEAEs: Subjects will be queried regarding ocular and nonocular AEs, SAEs, and changes in their general health, concomitant medications or concurrent procedures. Both elicited and volunteered reports will be recorded.

5.1 Measurements and Evaluations by Visit

The schedule of study procedures and assessments by visit is presented in Table 5–1. Study visits should be conducted within ±5 days for all scheduled visits.

Table 5–1: Schedule of Study Procedures and Assessments, Study EYP-1901-201

	Screening	Study Treatment and Follow-Up															
	Day -21 to -7	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56	ET[a]
Time Window (in days)			±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	
Informed Consent	X																
Inclusion/Exclusion Criteria	X	X															
Randomization		X															
Demographics	X																
Vital Signs[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X															X	X
Medical and Medication History	X																
Intraocular Pressure	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ocular Examination[c]	X	X	X	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Aflibercept Arm Dosing (study eye only)		E	E	E+S		E		E		E		E		E		E	
EYP-1901 Arms Dosing (study eye only)		E	E	E+I		S		S		S		S		S		S	
Post-Injection Intraocular Pressure[e]				X													
ETDRS BCVA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Color Fundus Photography	X	X		X			X			X			X			X	X
Fluorescein Angiography	X									X						X	X
SD-OCT Assessment	OU	SE	SE	SE	SE	SE	SE	SE	SE	OU	SE	SE	SE	SE	SE	OU	OU
SD-OCTA Assessment[f]	X									X						X	X
Clinical Laboratory Evaluations[g]	X			X			X			X			X			X	X
Urine Pregnancy Test[h]	X															X	X
Aqueous humor for PK[i]				SE			SE			SE							SE
Blood sampling for PK[i]				X			X			X			X			X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

BCVA = best corrected visual acuity; ECG = electrocardiogram; ETDRS = Early Treatment Diabetic Retinopathy Study; ET = early termination; IOP = intraocular pressure; PK = pharmacokinetic; SD-OCT = spectral-domain – optical coherence tomography; SD-OCTA = spectral-domain – optical coherence tomography angiography; VEGF = vascular endothelial growth factor; Wk = week

Note #1: All bilateral procedures and assessments are indicated by cells shaded gray

Note #2: During unscheduled visit or if posterior inflammation is present in study eye, CFP and OCT of study eye should be collected at a minimum

Note #3: X = study assessment; OU = both eyes; SE = study eye only; E = Eylea (aflibercept) treatment; S = sham treatment; I = EYP-1901 treatment

(table footnotes on next page)

Footnotes for Table 5-1:

a. Subjects who terminate the study prior to the Week 56 (End of Study) visit should undergo all procedures noted for the Early Termination Visit.

b. Vital signs will include pulse rate, respiratory rate, body temperature, and systolic and diastolic blood pressure (average of 3 readings will be taken in a resting state).

c. Anterior and posterior segments ocular examination.

d. Check central retinal artery perfusion following study injection.

e. At Week 8: measure IOP at 10 (+/- 5) and 60 (+/- 10) minutes following the second intravitreal injection (i.e., EYP-1901 or sham injection). If IOP measurements at any study time points are ≥30 mmHg, two additional measurements should be performed and IOP recorded as a mean of three measurements.

f. Spectral-domain – optical coherence tomography angiography (SD-OCTA) or swept-source – optical coherence tomography angiography (SS-OCTA) imaging to be collected at these time points at pre-specified study sites where SD-OCTA equipment is available.

g. Clinical laboratory testing will include hematology, serum chemistry, coagulation, and urinalysis evaluations (refer to the Study Laboratory Manual).

h. Females of childbearing potential only. Positive urine pregnancy results will be confirmed by a serum pregnancy test.

i. Pharmacokinetic analyses of vorolanib and its main metabolite will be performed on blood plasma and aqueous humor (study eye only) samples.

j. Adverse events, ocular and non-ocular, will be collected from the time the informed consent is signed. However, for safety analysis, only treatment-emergent adverse events (TEAEs) will be summarized.

5.1.1 Day -21 to Day -7 (Screening Visit)

The following procedures must be completed during the initial Screening Visit (Table 5–1):

Informed Consent: Properly executed informed consent (written and verbal) is to be obtained prior to completion of any trial related procedures. A subject may take as long as needed to review the informed consent form (ICF) and consider trial participation; they may take the document with them and return at a later date (provided the study is still open for enrollment). The subject must review, sign and date the document, and receive a copy.

Inclusion/Exclusion Criteria: Inclusion/exclusion criteria (Section 4.1 and Section 4.2, respectively) will be reviewed to determine the subject's eligibility to participate in the trial with the investigator verifying enrollment eligibility.

Demography, Medical History, and Medication History: Demography, complete medical history, and recent (previous 30 days) medications (Section 6.6.1) are to be recorded. When available, sites will provide pre-study OCT images collected at the time of original diagnosis of wet AMD, 1 month following the first intravitreal anti-VEGF injection, and those collected during the 9 months prior to study screening. Current contact lens use or ocular trauma in the study eye must be documented.

Ocular procedures to be performed with data collected for both eyes:

- ETDRS BCVA (Appendix 1)
- IOP (Appendix 2)
- Ocular examination – dilated ophthalmoscopy and slit lamp biomicroscopy (Appendix 2)
- CFP
- FA
- SD-OCT assessment (both eyes)
- SD-OCTA assessment (at pre-specified study sites where equipment is available)

Non-ocular procedures to be performed:

- Vital sign measurements (Section 7.3)
- ECG (Section 7.4)
- Collect blood and urine samples for clinical laboratory evaluations (Section 7.2)
- Urine pregnancy test
- Use of concomitant medications (Section 7.5)
- Adverse events, which will be collected from the time the ICF is signed (Section 7.1)

5.1.2 Day 1 (Randomization and Aflibercept Dosing)

The following procedures will be completed during the Day 1 visit (Table 5–1).

Inclusion/exclusion criteria (Section 4.1 and Section 4.2, respectively) will be reviewed again to confirm the subject's eligibility to keep participating in the trial, with the investigator verifying eligibility.

If meeting the eligibility criteria, study subjects will be randomized to study treatments and all subjects will receive the first dose of aflibercept (2 mg) in the designated study eye on Day 1. Aflibercept will be administered to the study eye of all subjects, irrespective of treatment arm, by injection through the pars plana (Section 6.2.2). Additionally, historical OCT images in original format for the 9 months prior to Screening are to be submitted to the central reading center. In the event that images are not available in the original format of capture, PDFs of the OCTs may be submitted.

For subjects with unilateral wAMD, the study eye will be the affected eye; for subjects with bilateral wAMD, the study eye will be the more severely affected eye meeting the inclusion/exclusion criteria (i.e., the eye having the worse BCVA or if equal, the eye clinically judged to be the more severely affected eye by the investigator). If the eyes are symmetrically affected, the study eye will be the right eye.

Ocular procedures to be performed with data collected for both eyes (unless otherwise specified):

- ETDRS BCVA (Appendix 1)
- IOP (Appendix 2)
- Ocular examination – dilated ophthalmoscopy and slit lamp biomicroscopy (Appendix 2)
- CFP
- SD-OCT assessment (study eye only)

Non-ocular procedures to be performed:

- Vital sign measurements (Section 7.3)
- Use of concomitant medications (Section 7.5)
- Adverse events (Section 7.1)

Throughout the study, unscheduled visit assessments may be performed as necessary at the discretion of the Investigator and following Sponsor approval. During an unscheduled visit or if posterior inflammation is present in study eye, CFP and OCT of the study eye should be collected at a minimum.

5.1.3 Week 4 (Aflibercept Dosing)

All study subjects will receive the second aflibercept dose (2 mg) in the designated study eye on Week 4, as described above in Section 5.1.2.

The following procedures will be completed during the Week 4 visit (Table 5–1).

Ocular procedures to be performed with data collected for both eyes (unless otherwise specified):

- ETDRS BCVA (Appendix 1)
- IOP (Appendix 2)
- Ocular examination – dilated ophthalmoscopy and slit lamp biomicroscopy (Appendix 2)
- SD-OCT assessment (study eye only)

Non-ocular procedures to be performed:

- Vital sign measurements (Section 7.3)
- Use of concomitant medications (Section 7.5)
- Adverse events (Section 7.1)

5.1.4 Week 8 (Aflibercept and EYP 1901 Dosing)

All study subjects will receive the third aflibercept dose (2 mg) in the designated study eye at Week 8, as described above and in Section 6.2.2; subjects assigned to EYP-1901 treatment arms will then receive the assigned EYP-1901 dose as bioerodible inserts 30 minutes (+/- 10 minutes) after receiving aflibercept and subjects in the aflibercept (control) treatment arm will receive a sham injection 30 minutes (+/- 10 minutes) later to maintain masking.

The following procedures will be completed during the Week 8 visit (Table 5–1).

Ocular procedures to be performed with data collected for both eyes (unless otherwise specified):

- ETDRS BCVA (Appendix 1)
- IOP, including post-injection (Appendix 2)
- Ocular examination – dilated ophthalmoscopy and slit lamp biomicroscopy (Appendix 2); check central retinal artery perfusion following study injection
- CFP
- SD-OCT assessment (study eye only)

Non-ocular procedures to be performed:

- Vital sign measurements (Section 7.3)
- Collect blood and urine samples for clinical laboratory evaluations (Section 7.2)
- Collect blood and aqueous humor (study eye only) samples for PK evaluation of the systemic and ocular exposure to EYP-1901 (Section 9)
- Use of concomitant medications (Section 7.5)
- Adverse events (Section 7.1)

5.1.5 Weeks 12, 28, 36, and 52 (Follow-Up Visits)

The following procedures will be completed during the Week 12, Week 28, Week 36, and Week 52 visits (Table 5–1).

Ocular procedures to be performed with data collected for both eyes (unless otherwise specified):

- ETDRS BCVA (Appendix 1)
- IOP (Appendix 2)
- Ocular examination – dilated ophthalmoscopy and slit lamp biomicroscopy (Appendix 2)
- SD-OCT assessment (study eye only)

Non-ocular procedures to be performed:

- Vital sign measurements (Section 7.3)
- Use of concomitant medications (Section 7.5)
- Adverse events (Section 7.1)

5.1.6 Weeks 16, 24, 32, 40, 48, and Week 56 (Aflibercept or Sham Dosing)

Study subjects assigned to the control group (aflibercept) will receive the subsequent aflibercept dose (2 mg) in the designated study eye (as described above in Section 5.1.2 and in Section 6.2.2) at a frequency of every 8 weeks after the Week 8 visit, specifically at the Week 16, Week 24, Week 32, Week 40, Week 48, and Week 56 visits, or when predefined re-treatment criteria are met (Section 6.6.4). Subjects in the EYP-1901 treatment arms will receive a sham injection at these visits to maintain masking (or aflibercept if the pre-defined re-treatment criteria are met).

The End of Study Week 56 visit procedures are described below in Section 5.1.8.

The following procedures will be completed during the Weeks 16, 24, 32, 40, and 48 visits (Table 5–1).

Ocular procedures to be performed with data collected for both eyes (unless otherwise specified):

- ETDRS BCVA (Appendix 1)
- IOP (Appendix 2)
- Ocular examination – dilated ophthalmoscopy and slit lamp biomicroscopy (Appendix 2)
- SD-OCT assessment (study eye only; except at Week 32, this will be performed in both eyes)

Non-ocular procedures to be performed:

- Vital sign measurements (Section 7.3)
- Use of concomitant medications (Section 7.5)
- Adverse events (Section 7.1)

In addition to the above, the following procedures will be completed during the Week 32 visit only:

- CFP
- FA
- SD-OCTA assessment (at pre-specified study sites where equipment is available)
- Collect blood and urine samples for clinical laboratory evaluations (Section 7.2)
- Collect blood and aqueous humor (study eye only) samples for PK evaluation of the systemic and ocular exposure to EYP-1901 (Section 9).

5.1.7 Weeks 20 and 44 (Follow-Up Visits)

The following procedures will be completed during the Week 20 and Week 44 visits (Table 5–1).

Ocular procedures to be performed with data collected for both eyes (unless otherwise specified):

- ETDRS BCVA (Appendix 1)
- IOP (Appendix 2)
- Ocular examination – dilated ophthalmoscopy and slit lamp biomicroscopy (Appendix 2)
- CFP
- SD-OCT assessment (study eye only)

Non-ocular procedures to be performed:

- Vital sign measurements (Section 7.3)
- Collect blood and urine samples for clinical laboratory evaluations (Section 7.2)
- Collect blood and aqueous humor (study eye only) samples for PK evaluation of the systemic and ocular exposure to EYP-1901 (Section 9). Aqueous humor will only be collected at the Week 20 visit.
- Use of concomitant medications (Section 7.5)
- Adverse events (Section 7.1)

5.1.8 Week 56 or Early Termination

As noted above in Section 5.1.6, study subjects assigned to the control group (aflibercept) will receive their final aflibercept dose (2 mg) in the designated study eye (as described above in Section 5.1.2 and in Section 6.2.2) at the Week 56 visit, or when predefined re-treatment criteria are met (Section 6.6.4). Subjects in the EYP-1901 treatment arms will receive the final sham injection at the end of study Week 56 visit to maintain masking (or aflibercept if the pre-defined re-treatment criteria are met).

The following procedures will be completed during the End of Study Week 56 visit (Table 5–1). Subjects who terminate the study prior to the Week 56 visit should undergo all procedures noted for the Early Termination Visit in Table 5–1.

Ocular procedures to be performed with data collected for both eyes:

- ETDRS BCVA (Appendix 1)
- IOP (Appendix 2)
- Ocular examination – dilated ophthalmoscopy and slit lamp biomicroscopy (Appendix 2)
- CFP
- FA
- SD-OCT assessment (both eyes)
- SD-OCTA assessment (at pre-specified study sites where equipment is available)

Non-ocular procedures to be performed:

- Vital sign measurements (Section 7.3)
- ECG (Section 7.4)
- Collect blood and urine samples for clinical laboratory evaluations (Section 7.2)
- Urine pregnancy test
- Collect blood samples for PK evaluation of the systemic exposure to EYP-1901 (Section 9).
- Use of concomitant medications (Section 7.5)
- Adverse events (Section 7.1)

5.2 Appropriateness of Measurements

The efficacy and safety assessments to be utilized in this study (e.g., use of concomitant medications, BCVA by ETDRS, slit lamp biomicroscopy, dilated ophthalmoscopy, IOP measurements, FA/CFP, SD-OCT, SD-OCTA [where equipment is available], collection of ocular and non-ocular AEs, clinical laboratory evaluations, vital signs, ECGs) are standard measures in studies evaluating intravitreal investigational products like EYP-1901.

6 STUDY INTERVENTIONS

6.1 Study Intervention Identification and Description

EYP-1901 intravitreal insert is a bioerodible, sterile, sustained-release drug delivery system that is designed to release microgram levels of vorolanib into the ocular vitreous chamber for the treatment of wAMD. The intravitreal insert formulation design is based on the Durasert® technology that allows EYP-1901 to exhibit the following characteristics:

- Bioerodible properties
- Sustained-release kinetics
- Prolonged duration of release (not less than 9 months)
- High drug loading

- Administration in an office setting through an intravitreal needle injection

EYLEA® is a marketed anti-VEGF solution containing aflibercept used to treat wAMD.

6.1.1 EYP-1901 Composition

EYP-1901 intravitreal insert contains vorolanib as the active ingredient and polyvinyl alcohol as an excipient.

The drug delivery system is placed into a one-time-use siliconized needle attached to an applicator delivery system. The drug product is sterilized after packaging and prior to distribution. In subject, the needle is inserted through the pars plana and the insert is injected into the vitreous.

Two different doses will be administered by delivering multiple inserts at Week 8 (Table 5–1). Table 6–1 summarizes the characteristics of the two intravitreal doses of EYP-1901.

Table 6–1: Characteristics of the Two Intravitreal Doses of EYP-1901

Dose (µg)	Number of Inserts per Single Applicator	Needle Gauge	Insert Length (mm)
2,060	2	22	8
3,090	3	22	8

6.1.2 Aflibercept Composition

EYLEA® contains aflibercept as the active ingredient in a clear to pale yellow aqueous solution (40 mg/mL aflibercept in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2) intended for use as a single 2 mg (0.05 mL) dose. The pre-filled syringe contains more than the recommended dose and the excess volume must be ejected prior to administration by depressing the plunger to align the plunger dome edge with a pre-marked dosing line found on the syringe.

EYLEA® comes in a sterilized blister pack and is equipped to attach to a 30-gauge injection needle (not provided with syringe). In subject, the needle is inserted through the pars plana and the aflibercept solution is discharged into the vitreous.

6.1.3 EYP-1901/Sham Applicator Packaging

EYP-1901 is packaged at EyePoint Pharmaceuticals. EYP-1901 loaded applicators (or sham applicators) are placed inside a foil chevron pouch and sealed. The sealed foil pouch is then placed inside a Tyvek® chevron pouch. The final pouch is sent for terminal sterilization. Upon completion of sterilization, each pouch is labeled with a “Sterile” label, and then placed into a labeled box.

6.1.4 Aflibercept Packaging

EYLEA® (aflibercept) is supplied as a 2 mg/0.05 mL solution in a single-dose pre-filled syringe or as a 2 mg/0.05 mL solution in a single-dose vial. Use of either format for this trial is acceptable.

6.2 Study Drug Administration

6.2.1 EYP-1901

Each EYP-1901 insert has been designed to deliver vorolanib into the vitreous humor for at least 9 months. EYP-1901 will be administered to the study eye by a single injection through the pars plana using a pre-loaded applicator with a 22-gauge needle.

6.2.2 Aflibercept

Aflibercept will be administered to the study eye by a single injection per standard of care.

Aflibercept will be administered initially to all subjects by intravitreal injection at a dose of 2 mg (0.05 mL) on Day 1 and at Week 4. At Week 8, all subjects will receive aflibercept and 30 minutes later will receive either a sham injection or EYP-1901, and if in the control group will resume aflibercept dosing at a frequency of once every 8 weeks (or when predefined re-treatment criteria are met) thereafter as the control treatment.

6.2.3 EYP-1901 Injection Procedure

For a detailed description of the EYP-1901 injection procedure, please refer to the EYP-1901 Instructions for Use document.

6.2.4 Aflibercept Injection Procedure

The same aseptic technique described above (Section 6.2.3) for EYP-1901 intravitreal injection procedure will be applied for the delivery of aflibercept, along with the standard of care for cleansing the eye (use of anesthetic, antibiotics, and Betadine®).

Aflibercept will be administered as detailed in the EYLEA® (aflibercept) label.

6.3 Storage and Dispensing of Study Drugs

EYP-1901 must be stored in a secure place and at controlled room temperature (20°C to 25°C/68°F to 77°F) and in the original container to protect the product from light. Temperature excursions between 15°C to 30°C/59°F to 86°F are acceptable.

Aflibercept must be stored in a secure place and refrigerated at a controlled temperature (2°C to 8°C/36°F to 46°F) and in the original carton to protect from light.

The Investigator has the overall responsibility of ensuring that EYP-1901 and aflibercept are stored in a safe location with limited-access under the specified storage conditions. Limited responsibility may be delegated to a pharmacy representative; however, this delegation must be documented.

6.4 Drug Accountability

The Investigator is responsible for ensuring adequate accountability of all used and unused EYP-1901 and aflibercept. While the Investigator may delegate components of drug accountability tasks to documented designee(s) (e.g., pharmacist or staff designee), the ultimate responsibility for drug control and accountability resides with the Investigator. This includes acknowledgment of receipt of each shipment (quantity and condition), maintenance of subject dispensing records and returned (as required) documentation. Dispensing records will document quantities received from the Sponsor (or designee) and quantities dispensed to subjects, including treatment kit/package number, date dispensed, subject identification number, subject initials, and the initials of the person dispensing drug will be recorded on the drug accountability log.

During study initiation, the study monitor (Clinical Research Associate, CRA) will evaluate and obtain a copy of each site's written standard operating procedure for study drug disposal/destruction or return to ensure that it complies with Sponsor requirements if supplies will not be returned.

An inspection for inventory and accounting purposes, and the assurance of proper storage, will also be conducted during monitoring visits. Any significant accounting or storage discrepancy will be recorded and reported to the Sponsor and a plan for resolution will be documented. After the monitor has checked and verified drug accountability during interim site visits and at the end of the study, any expired, partially-used, and used product should be handled according to the Sponsor's instructions (i.e., returned or destroyed).

6.5 Anaphylaxis, Overdose, and Dose Modification

Vorolanib and the inactive ingredients of EYP-1901 are not known to cause hypersensitivity reactions. Aflibercept is rarely associated with hypersensitivity, having been previously reported in less than 1% of patients.

Since EYP-1901 and aflibercept are delivered through a pre-loaded applicator or a syringe, respectively, the risk of accidental overdose is minimal. Refer to the current IB or FDA label for information on potential risks associated with EYP-1901 or aflibercept. Dose modification is not applicable since EYP-1901 and aflibercept are for single-delivery only.

Note: Hypersensitivity reactions to iodine and/or fluorescein used during ocular assessments are also possible.

Signs and symptoms of hypersensitivity include:

- Localized or generalized itching
- Facial flushing, generalized flushing
- Shortness of breath, wheezing
- Uneasiness and agitation
- Local edema followed by facial edema
- Light-headedness/dizziness
- Chest tightness

- Tachycardia
- Hypotension
- Rigors (chills)

If anaphylaxis occurs, the subject should be managed according to standard cardiopulmonary resuscitation (CPR) procedures, as necessary. The subject may require the following treatment:

- Epinephrine (adrenaline) to reduce the allergic response
- Oxygen
- Intravenous antihistamines and cortisone to reduce airways inflammation and improve breathing
- A beta-agonist (such as albuterol) to relieve breathing symptoms

6.6 Prior and Concomitant Medications

6.6.1 Prior Medications

Prior medications are defined as all prescription, vaccinations, supplements, herbal therapies, any prohibited medications, and over-the-counter (OTC) medications taken within the 30 days (whether continuing or not) prior to Day 1 with the exception of previous treatments for wAMD, both approved and investigational products. Previous treatments for wAMD are to be captured for the following timepoints: initial treatment upon diagnosis, 1 month after diagnosis, and for 12 months prior to Screening.

All prior medications must be documented on the concomitant medications eCRF.

6.6.2 Concomitant Medications

All prescription and OTC concomitant medications used concurrently (from the Screening Visit to Week 56 or Early Termination) must be documented on the concomitant medication eCRF.

Information to be collected on the concomitant medication eCRF includes the name of the medication/therapy, dose, frequency, route, dates of use, and indication for use. Subjects should be instructed not to take any medication including OTC products without first consulting with the Investigator. Any AE(s) that result(s) from taking a concomitant medication following the first study dose should be recorded on the AE eCRF.

6.6.3 Prohibited Concomitant Medications

Any medications or therapies that the subject is using during the study period and that would preclude eligibility as indicated in the Exclusion Criteria (Section 4.2), are prohibited concomitant medications. In addition, any medication or therapies initiated during the study period that, in the Investigator's judgment, could potentially confound the safety and preliminary efficacy of EYP-1901 or aflibercept would also be considered prohibited concomitant medications.

All prohibited concomitant medications used concurrently (from Day 1 to Week 56 or Early Termination) must be documented on the concomitant medication eCRF.

6.6.4 Rescue Treatment

Following the intravitreal injections of either dose of the EYP-1901 insert (2,060 µg or 3,090 µg) and aflibercept (2 mg) at Week 8, aflibercept may be administered in the study eye at the Investigator's discretion starting from Week 12 if at least one of the following criteria is met:

- BCVA reduction of ≥5 letters from best on study measurement due to wAMD
  AND
  Increase in CST of ≥75 microns on SD-OCT from lowest on study measurement
- BCVA reduction of ≥10 letters from best on study measurement due to wAMD
- Increase in CST of ≥100 microns on SD-OCT from lowest on study measurement from two consecutive visits
- Presence of new or worsening vision-threatening hemorrhage due to wAMD

If the above rescue criteria are not met, the Investigator may still determine the need for administering a rescue medication in the best interest of the subject's welfare. In this case, the Investigator is required to contact the Medical Monitor prior to rescue if feasible. The use of rescue medication during the study will be documented on the concomitant medication eCRF. Repeat administration following the first rescue intervention may be required if any of the rescue criteria are met again at any subsequent study visit. Subjects receiving rescue medications will continue in the study follow-up (Table 5–1).

Rescue therapy, other than aflibercept, is prohibited. Should aflibercept be given as rescue therapy at a visit that dosing was not scheduled (i.e., between the 8-week intervals of dosing after Week 12), the subject will continue with the subsequent dosing at the next scheduled visit, as the interval between both doses will be 4 weeks, which is acceptable as per approved dosing regimens. These subjects will then continue with the dosing regimen of every 8 weeks.

7 ASSESSMENT OF SAFETY

Safety assessments will include the incidence and severity of TEAEs reported after screening, clinical laboratory evaluations (hematology, serum chemistry, coagulation, and urinalysis), safety data collected from ocular examinations and IOP measurements, vital sign measurements, ECGs, and the use of concomitant medications.

Medical safety reviews will be conducted by the Sponsor for all TEAEs and other relevant information related to safety on an ongoing basis and throughout the duration of the study according to the study Safety Management Plan.

7.1 Adverse Events

The following are specific definitions of terms guided by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH E2), Guidelines for Good Clinical Practice (GCP), and the US Code of Federal Regulations (CFR) that apply to the following sections. The severity of AEs will be graded by CTCAE version 5 or higher (Appendix 4).

Definition of Adverse Event:

An AE is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational or marketed (medicinal) product and that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the product.

AEs may also include pre- or post-treatment complications that occur as a result of protocol-specified procedures (e.g., invasive procedures such as venipuncture, delivery procedure, etc.). Pre-existing conditions that increase in severity or change in nature during (or as a consequence of use of a medicinal product) the study will also be considered AEs.

An AE Will Not Include:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) for events that led to the procedure
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected prior to the Screening Visit, unless they worsen during the study
- Situations where an AE or untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)

Associated with the Use of the Drug (Causality):

There is a reasonable possibility that the event may have been caused by the study medicinal product (and/or the administration procedures).

Unexpected Adverse Event:

Any event that is not identified in nature, severity, or frequency in the current version of the IB; or in the product labeling for marketed products. For example, if the IB or product labeling referred to elevated hepatic enzymes or hepatitis, then an event of hepatic necrosis would be considered unexpected by the virtue of the greater severity. The Sponsor or designee will determine AE expectedness.

7.1.1 Ocular Adverse Events

The following ocular events will be considered AEs for the purposes of this study:

- Decrease in BCVA of ≥15 letters or ≥3 lines from the previous BCVA measurement
- Moderate or severe (Grade 2 or 3) ocular findings compared to the last ocular examination
- Worsening of >2 steps in anterior chamber cell count or vitreous haze compared to the last ocular examination
- Increase in IOP of >10 mmHg at two visits at least 1 week apart or an increase in IOP to >25 mmHg

7.1.2 Serious Adverse Events

An SAE is any AE that results in one of the following outcomes:

- Death.
- Is life-threatening (the term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more intense).
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons for any length of time), or prolongs existing hospitalization.
- Results in a persistent or significant disability/incapacity, or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect (in the child of a subject who was exposed to the study treatment).
- Other important medical event. Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization but required medical intervention in order to prevent a SAE outcome. However, if it is determined that the event may jeopardize the subject and/or may require intervention to prevent one of the other SAE outcomes, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The following hospitalizations will not be considered SAEs:

- A visit to the emergency room or other hospital department for <24 hours that does not result in in-patient admission (unless considered an "important medical event" or a "life -threatening event").
- Elective surgery or planned surgery prior to signing the ICF.
- Admissions as per protocol for a planned medical/surgical procedure.
- Routine health assessments requiring admission for Baseline/trending of health status (e.g., routine colonoscopy).
- Medical/surgical admission for a purpose other than healthcare purposes and was planned prior to entry into the study (appropriate documentation is required in these cases).
- Admission encountered for another life circumstance that carries no bearing on health status and/or requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).
- Progressive disease (wAMD) is expected and will not be considered an SAE.

Clarification of SAEs:

- Death is an outcome of an AE, and not an AE in itself.

- All deaths, regardless of cause or relationship, must be reported.
- Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is an SAE.
- "In-patient hospitalization" means the subject has been formally admitted to a hospital for medical reasons for any length of time. This may or may not be overnight. It does not include presentation to, and/or care within, an emergency department.
- The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information.

Note: Progressive disease should be recorded on the AE eCRF. However, because it is expected in the study population, it will not be considered as an SAE.

7.1.3 Sight-Threatening Ocular Events Defined as SAEs in This Study

In addition to the standard SAE categories described above, this study defines these additional ocular events as SAEs:

- An AE that causes a decrease in visual acuity of ≥30 letters or ≥6 lines from the most recent previous measurement of visual acuity, lasting more than 1 hour.
- An AE that causes a decrease in visual acuity to light perception or worse, lasting more than 1 hour.
- An AE that requires surgical intervention (e.g., conventional surgery, vitreous tap or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight.
- An AE that is associated with severe intraocular inflammation (i.e., 4+ anterior chamber cell score or 4+ vitreous haze score).
- Two consecutive IOP measurements of ≥30 mmHg taken at least 72 hours apart when a subject is already being treated with two IOP-lowering medications.
- An IOP <6 mmHg requiring medical intervention.
- An AE that in the opinion of the investigator requires medical or surgical intervention to prevent permanent loss of sight.

The Investigator must employ all necessary therapeutic measures to resolve the SAE. Any medications or therapies used to treat the SAE must be recorded in the concomitant medication eCRF.

7.1.4 Clinical Laboratory Adverse Events

An abnormal laboratory result should be considered an AE if it:

- Results in the initiation or change of an intervention (e.g., increased dose of medication), based on medical evaluation (e.g., packed red cells for low hemoglobin).
- Results in any out of range laboratory value that in the Investigator's judgment fulfills the definitions of an AE.

- Increases in severity compared to baseline.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the AE eCRF. It is the responsibility of the Investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

All laboratory AEs should be repeated and reassessed by the Investigator to track resolution and especially to confirm if they meet the definition of serious. If serious, they will be reported as SAEs.

The Investigator or a licensed designee must review all laboratory results in a timely manner as demonstrated by signature/date.

7.1.5 Adverse Event Severity and Relationship

Adverse event severity is defined as a qualitative assessment of the intensity of an AE as determined by the Investigator. The assessment of severity is made irrespective of the relationship or seriousness of the event to EYP-1901, aflibercept, or the injection device.

In the absence of an assigned severity per the CTCAE version 5.0 or higher (Appendix 4) grading criteria, the Investigator will grade AEs according to the following severity criteria:

Mild/Grade 1: the event may be noticeable to subject; does not influence daily activities; usually does not require intervention.

Moderate/Grade 2: the event may be of sufficient severity to make subject uncomfortable; performance of daily activities may be influenced; intervention may be needed.

Severe/Grade 3: the event may cause severe discomfort; usually interferes with daily activities; subject may not be able to continue in the study; treatment or other intervention usually required.

Life- or Sight-Threatening/Grade 4: the event requires urgent intervention to preserve life and/or permanent loss of vision.

Death/Grade 5: the event resulted in the subject's death.

Causality/Relationship to Study Treatment

The relationship of study treatment (i.e., EYP-1901 or aflibercept), the applicator, or the injection procedure, to each AE must be determined by the Investigator according to the following:

Not Related: Evidence indicates no plausible direct relationship to the study treatment, device, or procedure, or there is a reasonable causal relationship between non-study product, concurrent disease, or circumstance and the AE; and/or a causal relationship is considered biologically implausible.

Possibly Related:	There is reasonable causal relationship between the study treatment, device, or procedure and the AE. There may or may not be a clinically-plausible temporal sequence between the onset of the AE and study treatment, device, or procedure; the AE is not reasonably supported by other conditions.
Probably Related:	The study treatment, device, or procedure and AE occurrence are reasonably related in time; a clinically-plausible temporal sequence between the onset of the AE and study treatment, device, or procedure is likely; based upon the Investigator's clinical experience, the association of the AE with study treatment, device, or procedure is likely; all other potential causes have been ruled out.

If the relationship between the AE/SAE and the sequence study treatment, device, or procedure is determined to be "possible" or "probable", the event will be considered related for the purposes of expedited regulatory reporting.

7.1.6 Recording of Adverse Events

Medical conditions or diseases present before a subject starts study treatment are only considered AEs if they worsen after the start of the study treatment.

Adverse events may be spontaneously reported or elicited at each study visit through open-ended questioning, examination, or evaluation of a subject. To prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.

The Investigator will record all AEs in the eCRF. Where a diagnosis is possible, it is preferable to report the diagnosis rather than a series of terms (signs/symptoms) relating to the diagnosis. If a definitive diagnosis is not possible, the individual symptoms and signs should be recorded.

The following information must be captured for all AEs:

- Onset and end date
- Severity
- Seriousness
- Relationship to EYP-1901, aflibercept, the injection device, or the procedure
- Action taken
- Any treatment required
- Outcome

If treatment for the AE was administered, it should be recorded on the appropriate concomitant medication/procedure eCRF page. Each distinct AE should be recorded separately.

7.1.7 Adverse Event Reporting

All subjects enrolled in the study will be evaluated for AEs, which will be collected from the time the ICF is signed until study completion (Table 5–1).

All AEs will be evaluated from onset until resolution or stabilization, whichever is first. Adverse events that continue after the subject's discontinuation or completion of the study will be followed until their medical outcomes are determined or until no further change in the condition is expected. The event and outcome will be reported in writing by the Investigator to the Sponsor. The Investigator shall supply the Sponsor and Institutional Review Board (IRB)/Ethics Committee (EC) with any additional requested information, notably for reported deaths.

7.1.7.1 Reporting of Serious Adverse Events

All SAEs, regardless of cause(s) or relationship to study drugs, must be recorded on the appropriate eCRF page and reported to the Sponsor within 24 hours of the Investigator's first awareness using the study's designated SAE/SADR (Serious Adverse Drug Reaction) Report Form.

Minimal information to be provided on the SAE/SADR Report Form includes:

- Protocol number
- Site and Investigator identifiers
- Subject number
- Brief description of the event(s)
- Onset date of the event
- Outcome of the event as of the date of report, if known
- Resolution date and time, if the event(s) resolved
- Any medication administered to treat the event
- Investigator's assessment of the causal relationship of the SAE to the study medicinal product
- Additional and follow-up information as requested by Sponsor or its designee

SAEs must be reported using the study's designated SAE/SADR Report Form and sent to:

Email: PPD

Fax: PPD

The Investigator will also compile other relevant documentation with urgent priority (e.g., copies of test results, hospital discharge summary, autopsy report, etc.), and send this information to the Sponsor (or Sponsor's designee).

The FDA and all participating Investigators shall be notified by a written Investigational New Drug Application (IND) safety report of any AE associated with the use of the investigational product that is both serious and unexpected no later than 15 calendar days from the Sponsor's awareness date of the event. An SAE is considered to be associated with the use of the investigational product if the relationship between the SAE and the investigational product is classified by the Investigator as "possibly related" or "probably related" (i.e., suspected, unexpected serious adverse reaction [SUSAR]). Any unexpected fatal or life-threatening SAE associated with the use of the investigational product will be reported to the FDA by the Sponsor within 7 calendar days.

The IRB/EC should be notified of SAEs as required in accordance with the local institutional policy.

All Investigators participating in the study will be notified of unexpected SAEs determined to be related to study treatment/injection procedure.

Pregnancy

Pregnancy that occurs during the study must be immediately reported to the Investigator who will immediately notify the Sponsor or designee within 24 hours of first awareness using the study's designated Pregnancy Report Form. This includes any pregnancy following maternal or paternal exposure to the study treatments.

The pregnancy should be followed to term. The outcome, including premature termination must also be reported to the Sponsor or designee within 24 hours of the Investigator's awareness using the Pregnancy Report Form. All live births must be followed for a minimum of 4 weeks or to the first well-baby visit. All reports of congenital abnormalities/birth defects and spontaneous abortions/miscarriages should be reported as SAEs. Elective abortion procedures without complications should not be considered as AEs.

If the Investigator becomes aware of a pregnancy occurring in any male subject's partner during the male subject's treatment with the assigned study medicinal product, the Investigator must submit this information to the Sponsor on the Pregnancy Report Form.

The Pregnancy Report Form should be sent to:

Email: PPD

Fax: PPD

Special Situations

Notification must be made to the Sponsor or designee of any special situation which includes the following, regardless of any associated AE:

- A medication error, defined as any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider or subject.
- Abuse, defined as persistent or sporadic intentional excessive use of a medicinal or other product.
- Misuse, defined as any intentional or inappropriate use of a medicinal product that is not in accordance with the protocol instructions or local prescribing information.
- An overdose, defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose per protocol or in the product labeling. In cases of a discrepancy in drug accountability, overdose will be determined only when it is clear that the subject received an excess dose(s).

Special situations should be reported on the study's designated SAE/SADR Report Form except pregnancies for which there is a dedicated form. If any special situation results in clinical sequela(ae)/AE(s), the event(s) must be recorded on the AE eCRF. If the AE is serious, the SAE

eCRF must be completed and a SAE/SADR Report Form must be completed and submitted to the Sponsor or designee within 24 hours of first awareness.

Special situations involving concomitant medication do not need to be reported on the SAE/SADR Report Form. However, special situations involving concomitant medication that result in clinical sequelae/AEs should be reported on the AE eCRF. In addition, any inappropriate use of prohibited concomitant medications should not be reported as "misuse" but may be more appropriately documented as a protocol deviation.

Using the SAE/SADR Report Form, reports of special situations should be sent to:

Email: PPD

Fax: PPD

7.2 Clinical Laboratory Evaluations

The clinical laboratory tests listed in the Study Laboratory Manual, including hematology, serum chemistry, coagulation, and urinalysis parameters, will be performed at the study visits indicated in Table 5–1.

A central laboratory will be used to measure laboratory parameters. The Investigator will use these results for clinical purposes and the laboratory data will be used for safety analyses. Normal value ranges and laboratory certification will be collected prior to study initiation.

Investigators must review and document laboratory test results, as well as address the clinical significance and causality (for significant abnormalities). Clinically significant abnormal laboratory results should be repeated as soon as possible. Section 7.1.4 provides further guidance as to when abnormal laboratory results are to be reported as AEs.

7.3 Vital Signs

Vital signs will include pulse rate, respiratory rate, body temperature, and systolic and diastolic blood pressure (average of 3 readings will be taken in a resting state) at the visits indicated in Table 5–1.

7.4 Electrocardiograms

Standard 12-lead ECG assessments will be performed at visits indicated in Table 5–1.

7.5 Concomitant Medication Use

During the study, rescue treatment with aflibercept for the progression of wAMD may be required in the study eye for some subjects as a result of AEs or lack of efficacy of the study treatment. Rescue treatment will be allowed per pre-specified rescue criteria (Section 6.6.4). If the rescue criteria are not met, the medications will be considered prohibited medications. Prohibited medications (Section 6.6.3), although discouraged, can be used if necessary (e.g., no other alternative) but will be considered protocol deviations. Information regarding concomitant medication use will be collected at the visits specified in Table 5–1.

8 REPORTING OF TECHNICAL PRODUCT COMPLAINTS

A Product Complaint (PC) is defined as any written, electronic, or verbal expression of dissatisfaction regarding the identity, quality, reliability, safety, purity, potency, effectiveness, or performance of an investigational or commercial product after it is released for distribution (e.g., any failure of the applicator to deliver the intravitreal insert), or dissatisfaction with any other characteristic(s) of the drug product (e.g., labeling, packaging, etc.).

Any/all PCs should be reported to EyePoint within 24 hours using the designated PC Report Form. The complaint report should include the following information:

- Product identification number
- Investigator name, study site name, and contact phone number
- Date the complaint occurred
- Brief description of the complaint
- Subject involved? (yes or no); if yes, were any AEs associated with the complaint? (yes or no). If (yes) an AE is associated with the complaint, please refer to Section 7.1

PPD

The drug container (applicator, foil pouch, and carton) for which the complaint was initiated should be retained for return to EyePoint at the address below for analysis.

Attention:

Product Returns
EyePoint Pharmaceuticals, Inc.
480 Pleasant Street
Watertown, MA 02472 USA

Any complaint about an investigational product must be reported regardless of whether the defect or deficiency had any effect on a subject or on study personnel.

9 PHARMACOKINETICS

Secondary endpoints in this study include the evaluation of the systemic and ocular exposure to EYP-1901 as measured through plasma and aqueous humor levels in the study eye, respectively, of vorolanib and its main metabolite. Blood and aqueous humor samples will be collected at the visits noted in Table 5–1 for PK analysis of vorolanib and its main metabolite concentrations. Collection, handling, storage, and shipment of samples to the designated analytical testing laboratory will be conducted according to the procedures described in Appendix 3.

In the event the subject requires vitrectomy during the study, the unmasked investigator or designee will collect a vitreous sample and EYP-1901 implants (if applicable) to be sent to sponsor as described in Appendix 3.

10 ASSESSMENT OF EFFICACY

The primary endpoint of this study is to evaluate the efficacy of EYP-1901 vs. aflibercept in wAMD, specifically the average change in BCVA from Day 1 averaged over Week 28 and Week 32.

Additional efficacy endpoints are assessed as part of the secondary objectives described in Section 2.

Statistical analysis of the efficacy endpoints is described below in Section 11.4.4.

11 STATISTICAL METHODS AND DATA ANALYSIS

Detailed methodology for statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be developed and maintained by the Sponsor.

The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

All study data will be presented in by-subject listings.

11.1 Determination of Sample Size

The primary objective of the study is to provide efficacy and safety data in a prospective, randomized, double-masked, controlled trial. The study will be unmasked upon completion of Week 32, at which point efficacy and safety endpoints will be analyzed for all randomized subjects. CCI [redacted]

11.2 Analysis Population

The intent-to-treat (ITT) population will include all subjects who received at least one dose of study treatments (aflibercept or EYP-1901). The safety summaries will be based on the ITT population. The subjects will be summarized based on the treatments that they actually receive.

The efficacy population will include all subjects who received at least one dose of study treatments (aflibercept or EYP-1901) and continue until at least Week 32 (i.e., have had the primary endpoint assessed).

11.3 General Statistical Considerations

11.3.1 Data Summarization

Data summaries for variables measured on a continuous scale will include descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) by treatment arm. Data will be pooled for all study sites for data analysis, unless otherwise specified.

For variables evaluated on a categorical scale, data summaries will include the number and percentage of subjects who provide each possible category, by treatment arm. The 95% confidence interval (CI) of the proportions will be constructed, as appropriate.

11.3.2 Definition of Baseline

Baseline measurements are those taken at Screening or prior to receiving study drug on Day 1, whichever is the latest.

11.3.3 Handling of Missing Data

In general, missing data will not be imputed, unless otherwise specified. Every effort will be made to ensure completeness of data collection.

11.3.4 Multicenter Considerations

Approximately 70 investigative study sites will participate in the study. All sites will be located in the United States. Due to the limited sample size, a site effect will not be analyzed, unless otherwise specified.

11.3.5 Adjustment for Covariates

Not applicable.

11.3.6 Interim Analyses

No interim analyses are planned for this study prior to the primary endpoint readout at Week 32.

11.3.7 Multiple Comparisons and Multiplicity

Not applicable.

11.3.8 Examination of Subgroups

Data will be summarized by treatment arm. Subgroup analyses could be performed upon completion of study follow-up and data collection as described in the SAP.

11.3.9 Statistical Software

All statistical summaries and analyses will be produced using SAS, Release 9.3 or higher.

11.4 Analyses

11.4.1 Subject Disposition

A summary table will be prepared indicating the number and percentage of subjects in each treatment arm and overall who were included in the ITT population. Within the ITT population, the number and percentage of subjects who did/did not complete the study will be presented. Screen failures, including reasons for failing to satisfy eligibility criteria will also be summarized.

Subjects who discontinue any time during the study will be categorized by reason for termination, and the percentage within each category will be provided.

11.4.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment arm and overall using descriptive statistics for the ITT population.

11.4.3 Medical History

Medical history will be coded and listed by treatment arm.

11.4.4 Efficacy Analysis

Primary Endpoint:

The average change in BCVA from Day 1 averaged over Week 28 and Week 32 will be descriptively summarized by treatment arm for the efficacy population. Further details will be described in the SAP.

Secondary Endpoints:

Descriptive statistics will be provided for the secondary endpoints by treatment arm for the efficacy population. Further details will be described in the SAP.

11.4.5 Pharmacokinetic Analysis

Descriptive statistics will be provided for plasma and aqueous humor PK data by treatment arm for the ITT population.

11.4.6 Adverse Events

Both ocular and non-ocular TEAEs are defined as events that start after the first study drug administration, and occur before termination of the study, or were present before first study drug administration and worsened after administration. Descriptive statistics will be provided for all TEAEs by treatment arm and overall for the ITT population.

Adverse events will be coded by System Organ Class (SOC) and preferred term (PT) using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Ocular and non-ocular TEAEs will be summarized separately. The number and percentage of subjects who experience an AE will be presented. Within each level of summarization (SOC, PT), subjects who experience more than one occurrence will only be counted once. Adverse events will also be presented by severity (mild, moderate, severe, life-threatening, fatal), and by relationship to study drug (not related, possibly related, probably related). Listings of deaths, SAEs, and withdrawals due to AEs will be presented.

11.4.7 Clinical Laboratory Evaluations

Clinical laboratory evaluations (hematology, serum chemistry, coagulation, and urinalysis) will be presented using descriptive statistics by treatment arm for the ITT population. Laboratory values will be listed by subject, and values outside of a normal reference range will be flagged. Pregnancy test results will be listed separately.

11.4.8 Vital Signs and Electrocardiograms

Vital signs (pulse rate, respiratory rate, body temperature, and systolic and diastolic blood pressure) and ECG results will be presented using descriptive statistics by treatment for the ITT population. Averages of replicate readings will be used in analysis. Listings of ECG and vital signs data will be provided.

11.4.9 Prior and Concomitant Medications

Medications for both ocular and non-ocular indications will be coded using the World Health Organization (WHO) Drug Dictionary. These medications (prescription, OTC, and nutritional supplements) will be summarized by anatomical therapeutic chemical (ATC) classification levels, WHO generic name, and treatment arm. Subjects will only be counted once at each level of the generic name or ATC level.

11.4.10 Use of Prohibited Medications

Prior to database lock, the Sponsor will conduct a blinded data review of concomitant treatments to determine if any fall under prohibited medications (Section 6.6.3). The proportion of subjects receiving these medications will be summarized by treatment arm and time point.

12 ADMINISTRATIVE AND REGULATORY CONSIDERATIONS

12.1 Quality Control and Quality Assurance

The Sponsor's employees and/or their contracted representatives utilize standard operating procedures (SOPs) designed to ensure that research procedures and documentation are consistently conducted/prepared to the highest quality standards. These SOPs also require compliance with Health Authority regulations and GCP guidance.

A Quality Assurance audit may be conducted by the Sponsor or a designee at any time during or after completion of this study. The Investigator will be given adequate notice if he/she is selected for an audit. The audit will include, but is not limited to, a review of all ICFs, a review of eCRFs, associated source documents and medical records, a review of regulatory documentation, an assessment of study conduct and protocol compliance, and a review of the investigational drug accountability. At the conclusion of an audit, the auditor will conduct a brief meeting with the Investigator to review the audit findings.

12.2 Institutional Review Boards/Independent Ethics Committee

Prior to the study initiation, the protocol and ICF will be submitted to the IRB/EC for approval. The IB may also be submitted as supplemental information. By signing the "Statement of Investigator" form (FDA form 1572), the Investigator is assuring that an IRB/EC that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review of the clinical study. A copy of the IRB/EC approval letter for the protocol, and the informed consent, as well as the protocol signature page must be submitted to the Sponsor or its designee prior to release of investigational supplies to the study site. The approval letter must refer to the specific protocol and informed consent form. The study site must maintain an accurate and complete record of all reports, documents, and other submissions made to the IRB/EC concerning this protocol. A list of the IRB/EC members, their titles or occupations, and their institutional affiliation, or an IRB/EC assurance number must be provided to the Sponsor or its designee prior to release of study supplies.

FDA/relevant health authority regulations require that all advertisements for subject recruitment be approved by an IRB/EC prior to implementation. The complete text and format must be submitted to the Sponsor or designee for approval prior to IRB/EC submission.

The Investigator is responsible for notifying the IRB/EC of any SAEs. A copy of the notification must be forwarded to the Sponsor or its designee.

Status reports must be submitted to the IRB/EC at least once a year (or more frequently as required by the IRB/EC) and the IRB/EC must be notified of study completion or termination. A final report must be provided to the IRB/EC and the Sponsor within 6 months of study completion or termination. This report should include: any protocol deviations, the number of subjects evaluated, the number of subjects who withdrew or were withdrawn and the reasons for withdrawal, any significant AEs, and the Investigator's summation of the study.

12.3 Informed Consent Process

It is the responsibility of the investigator to inform each subject, prior to the screening evaluation, of the purpose of this clinical trial, including possible risks and benefits and document the informed consent process in the subject's chart. Prior to entry into the study or initiation of any study-related procedures, the subject must read, sign and date the IRB/EC approved ICF. The person executing the consent must also sign and date the final consent form page. One or two signed originals of the ICF will be prepared, in accordance with applicable local requirements. A signed original copy will be retained with the subject records, and either a copy of the signed original or the other signed original of the ICF will be given to the subject, in accordance with applicable local requirements.

12.4 Source Documentation

The Investigator must maintain adequate and accurate source documents upon which eCRFs for each subject are based. These documents are to be separate and distinct from eCRFs, except for cases in which the Sponsor has predetermined that direct data entry into specified pages of the subject's eCRF is appropriate. The Investigator must allow access to the source documents by representatives of the Sponsor and regulatory authorities as needed. These records should include detailed notes on:

- The date the subject entered the study, study protocol number, and name of the Sponsor.
- The oral and written communication with the subject regarding the study treatment (including the risks and benefits of the study). The date of informed consent must be recorded in the source documentation.
- The subject's medical history prior to participation in the study and evidence that the subject meets study eligibility requirements.
- The subject's basic identifying information, such as demographics, that link the subject's source documents with the eCRFs.
- The dates of all study-related subject visits.
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject.
- The subject's exposure to study treatment, and documentation of study treatment accountability.
- All AEs.

- The subject's exposure to any concomitant therapy (including start and stop dates, route of administration, and dosage).
- All relevant observations and data on the condition of the subject throughout the study.
- The date when subject exited the study and a notation as whether the subject completed the study or was discontinued, including the reason for discontinuation.

Upon request, the Investigator will provide the Sponsor with any required background data from the study documentation or clinic records. This is particularly important when source documents are illegible or when errors in data transcription are suspected. In case there are issues or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

12.5 Electronic Case Report Forms

All study data must be incorporated in the corresponding eCRFs which are designed for computer processing and analysis. The Investigator will be responsible for recording all data in the eCRFs and must ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the eCRF and in all required reports.

Data from clinical laboratory reports, etc., will be incorporated into the eCRFs either by direct transcription into appropriate eCRF pages or by inclusion of photocopies of these reports with printouts of the appropriate eCRF pages and stored in the site's Study Binder.

If corrections are made following official final review and sign-off by the Investigator, the Investigator must be made aware of the changes and provide written acknowledgement.

This study will be conducted in compliance with the regulations contained within 21 CFR Part 11, electronic records/electronic signatures regulations.

12.6 Retention of Study Records

GCP regulations require that the Investigator retain all documentation related to this clinical trial for a period of 2 years after the approval of the NDA in the US (or Product License outside the US) for this drug or 2 years after the withdrawal of the IND. These records include the protocol and copies of all documents submitted to the Sponsor or to government authorities, subject records (including signed ICFs, subject charts, eCRFs, and other source documents), IRB/EC approvals and correspondence, records of drug accountability, and all study communications, whether written, telephonic, or electronic. None of the required documents will be destroyed or transferred to the control of another party without the written approval of the Sponsor.

If the Investigator cannot guarantee the archiving requirement at the site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in a sealed container outside of the study site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies will be made for storing outside of the study site.

12.7 Monitoring the Study and Data Quality Assurance

Representatives of the Sponsor (or designees) will contact the Investigator and his/her staff prior to the start of the trial to review the procedures to be followed in conducting the study and recording the findings, and to confirm the facility's readiness to conduct the trial.

It will be the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor must have access to all study related reports and records needed to verify the entries on the eCRF. The Investigator (or designee) must agree to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved and agree to provide missing information and grant access to all study documentation.

Every attempt must be made to follow the protocol, obtain and record all data requested for each subject at the specified times. However, ethical reasons may warrant the failure to obtain and record certain data or to record data at the times specified. If data is not recorded per protocol, the reasons must be clearly documented on the eCRF/records.

Accurate and reliable data collection will be ensured by the verification of the eCRFs against the Investigator's records by the monitor (source documentation verification). Collected data will be entered into a computer database and subject to electronic and manual quality assurance procedures.

The study data must be verifiable with the source data, which requires access to all original recordings, laboratory reports, product accountability records, including access to the subject electronic medical record, and source data must be made available for all study data. Subjects must also allow access to their medical records. They will be informed of this and must consent to permission by providing their signature on the ICF prior to enrollment.

Representatives of the Sponsor (or designees) may audit the study periodically to ensure that all records are correct and complete. The verification of the eCRF data must be by direct inspection of source documents.

12.8 Discontinuation of the Study

The Sponsor reserves the right to discontinue this study for administrative reasons at any time.

The trial may also be terminated prematurely if unexpected AEs occur or if the Investigator does not adhere to the protocol.

12.9 Policy for Publications

The detailed procedures for the review of publications are set out in the clinical trial agreement entered into with the Sponsor in connection with this study. Results from the study shall not be made available to any third party by the Investigator or staff outside of the publication policy.

13 ETHICS

13.1 Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB/EC as appropriate. The IB may also be provided as required. The Investigator must submit written approval from an IRB/EC to the Sponsor or a designee such as a Contract Research Organization (CRO) before the Investigator may initiate this study.

The Principal Investigator is responsible for informing the IRB/EC of any amendment to the protocol in accordance with local requirements. In addition, the IRB/EC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB/EC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor or the CRO will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/EC according to local regulations and guidelines.

13.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements.

13.3 Written Informed Consent

A properly executed, written informed consent document, in compliance with 21 CFR 50, the ICH guidelines, and relevant local regulatory requirements, will be obtained from each subject before the subject is enrolled into the study and before any study-related procedure is performed. Attention will be directed to the basic elements required for incorporation into the informed consent under US Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a]) and (21 CFR 50.25[b]).

The informed consent document will be reviewed by the Sponsor or designee for inclusion of all required elements prior to submission to the IRB/EC. The Sponsor must also review any revisions to the approved informed consent document prior to submission to the IRB/EC. The final IRB/EC-approved document must be provided to the Sponsor for regulatory purposes. It is the responsibility of the Investigator, or a person designated by the Investigator, to obtain written informed consent from each subject (or the subject's legally authorized representative) participating in the study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. In the case where the subject is unable to read the form, an impartial witness will be present during the entire informed consent discussion. After the subject has orally consented to participate in the study, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood.

A copy of the fully executed informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified

translation of the local language by the site under the guidance of the Investigator. Signed informed consent documents must remain in each subject's medical record and be made available for verification by the monitor at any time.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated as necessary. All subjects (including those who have already been treated with EYP-1901 during the study) will be informed of the new information and given a copy of the revised form to provide their consent in order to continue participation in the study.

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Yancopoulos GD. Clinical application of therapies targeting VEGF. Cell. 2010;143:13-16.

APPENDIX 1: MEASUREMENT OF BCVA BY ETDRS

Please refer to the BCVA Assessment Manual for the study.

APPENDIX 2: Slit Lamp Biomicroscopy, Ophthalmoscopy, and Intraocular Pressure

Slit Lamp Examination

A routine slit lamp examination will collect clinical findings from the anterior and posterior segment of both study and fellow eye with pupil dilation and should be conducted after IOP measurement has been completed.

Anterior Chamber Cell Grading Scale:

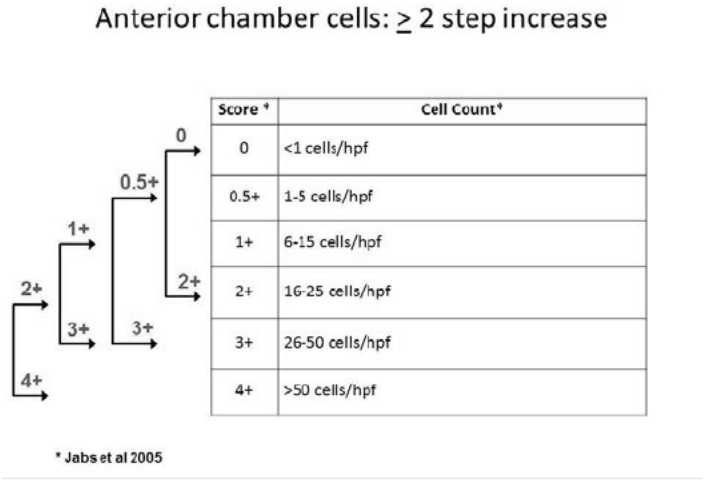
Anterior chamber cells will be measured using a Haag/Streit or similar slit lamp at high magnification (1.6 X) 1-mm beam. The same instrument, and when possible, the same examiner should be used on each patient throughout the study. Assessment will be made using the following scale (Jabs et al. 2005).

Field size: 1 mm by 1 mm slit beam

0	<1 cells/hpf
0.5+	1-5 cells/hpf
1+	6-15 cells/hpf
2+	16-25 cells/hpf
3+	26-50 cells/hpf
4+	>50 cells/hpf

Anterior Chamber Cell Scoring Convention

The diagram on the right presents the scoring convention that will be used to identify a "≥2 step increase" of anterior chamber cells.



Ophthalmoscopy

Ophthalmoscopy will be performed to assess retinal and choroid appearances and vitreous haze (Nussenblatt et al. 1985). Indirect ophthalmoscopy will be performed for study eye and fellow eye with pupil dilation and should be conducted after IOP measurement has been completed.

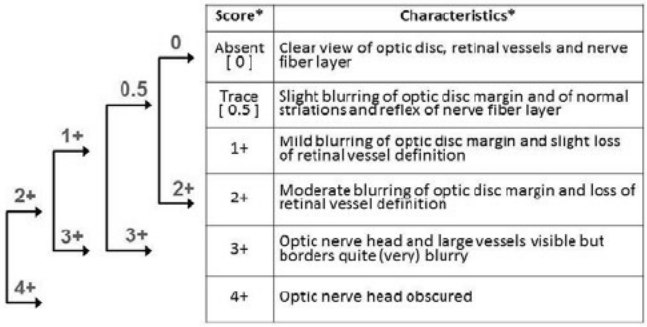
Vitreous Haze Grading Scale

The following scale will be used to define the extent of vitreous haze:

Absent	Clear view of optic disc, retinal vessels and nerve fiber layer
Trace	Slight blurring of optic disc margin and of normal striations and reflex of nerve fiber layer
1+	Mild blurring of optic disc margin and slight loss of retinal vessel definition
2+	Moderate blurring of optic disc margin and loss of retinal vessel definition
3+	Optic nerve head and large vessels visible but borders quite (very) blurry
4+	Optic nerve head obscured

Vitreous Haze Scoring Convention

The diagram on the right presents the scoring convention that will be used to identify a "≥2 step increase" of vitreous haze.



Fundus Examination

The fundus assessments should be conducted using indirect ophthalmoscopy with a 20 diopter, 28 diopter, or 30 diopter condensing lens. In order to minimize variability, every effort should be made to have a single examiner conduct all assessments on a given subject.

Intraocular Pressure

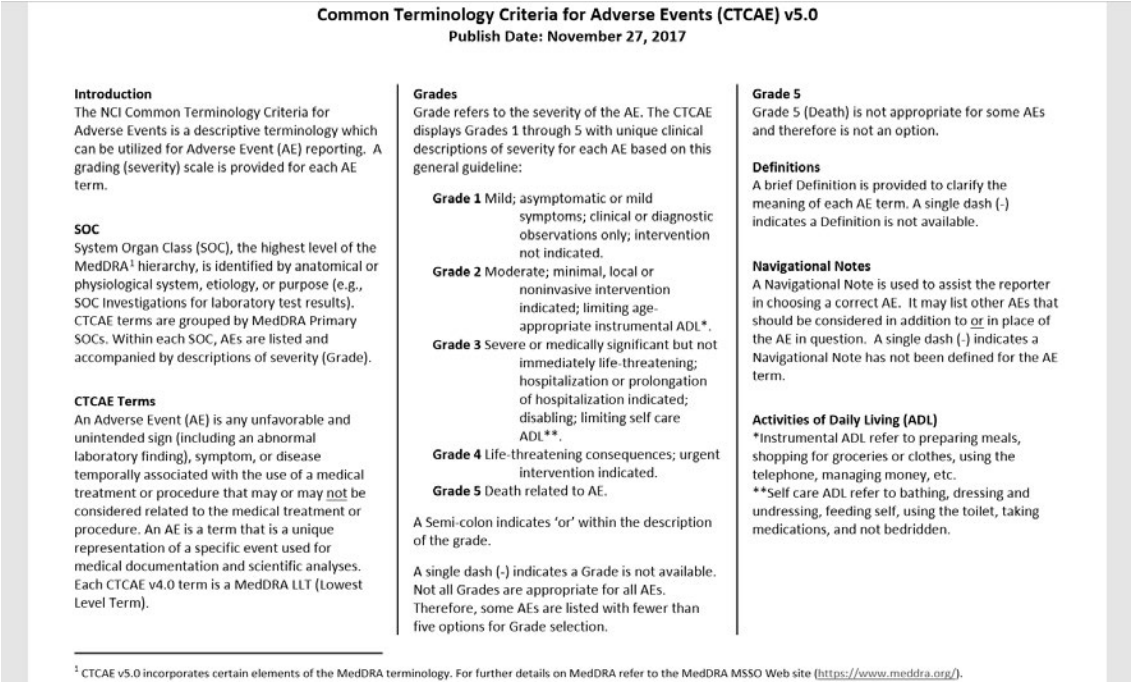
Intraocular pressure will be assessed by applanation tonometry (preferably, Goldmann) and should be measured before the slit lamp examination has been completed at all study visits, and at the Week 8 visit it should be measured at 10 (+/- 5) and 60 (+/- 10) minutes following the second intravitreal injection (i.e., EYP-1901 or sham injection). If IOP measurements at any study time points are ≥30 mmHg, two additional measurements should be performed and IOP recorded as a mean of three measurements per eye. All reasonable efforts should be made to have the same examiner obtain all IOP measurement for a given subject. Measurement should be performed before dilated ophthalmoscopy.

APPENDIX 3: Pharmacokinetic Procedures and Analysis

Please refer to the Lab Manual for the study.

APPENDIX 4: NCI CTCAE v5.0

Adapted from:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf



Common Terminology Criteria for Adverse Events (CTCAE) v5.0
Publish Date: November 27, 2017

Introduction
The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

SOC
System Organ Class (SOC), the highest level of the MedDRA[1] hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms
An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Grades
Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- **Grade 4** Life-threatening consequences; urgent intervention indicated.
- **Grade 5** Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a Grade is not available. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5
Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Definitions
A brief Definition is provided to clarify the meaning of each AE term. A single dash (-) indicates a Definition is not available.

Navigational Notes
A Navigational Note is used to assist the reporter in choosing a correct AE. It may list other AEs that should be considered in addition to or in place of the AE in question. A single dash (-) indicates a Navigational Note has not been defined for the AE term.

Activities of Daily Living (ADL)
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

[1] CTCAE v5.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (https://www.meddra.org/).

APPENDIX 5: Summary of Changes

The following changes were made to Protocol EYP-1901-201 as Amendment 1 (v2.0):

SECTION(S)	CHANGE/RATIONALE
Synopsis Section 2 Section 3.1 Section 3.4 Section 5.1.7 Table 5–1 Schedule of Assessments	• End of Study visit was changed from Week 60 to Week 56, which allows for a 48-week follow-up from EYP-1901 administration.
Synopsis Section 2 Section 10 Section 11.4.4	• The primary endpoint was changed from "Change in BCVA from Day 1 to Week 32" to "Average change in BCVA from Day 1 averaged over Week 28 and Week 32", which allows for a blended BCVA to reduce variability.
Synopsis Section 2 Section 10	• The secondary endpoints were updated to reflect the new end of study at Week 56 instead of Week 60.
Synopsis Section 3.2	• The unmasking of study data at Week 32 was clarified.
Section 3.4 Section 5.1.1 Table 5–1 Schedule of Assessments	• Duration of the Screening Period was changed from Days -14 to -7 to Days -21 to -7, to allow Investigators more time to evaluate potential subjects.
Synopsis Section 4.2	• Exclusion criteria #7 (regarding intraretinal fluid at Screening) and #36 (regarding HbA1c at Screening) were clarified.
Section 5 Section 5.1.2	• Added a new study requirement for historical OCT images in the original format for the 9 months prior to Screening to be submitted to the central reading center. In the event that images are not available in the original format of capture, PDFs of the OCTs may be submitted.
Section 6.1.4	• Clarified that EYLEA® (aflibercept) is supplied as a 2 mg/0.05 mL solution in a single-dose pre-filled syringe or as a 2 mg/0.05 mL solution in a single-dose vial, and that either format is acceptable for use in this study.
Section 6.2.3	• Removed reference of study manual for injection procedure.
Synopsis Section 6.6.4	• Rescue treatment criteria were reordered and clarified.
Section 11.4.8	• Added ECG results to the statistical analysis sections.
Table 5–1 Schedule of Assessments	• The Schedule of Assessments table was completely revised to reflect the change from Week 60 to Week 56 End of Study visit. • The footnotes for Table 5-1 were also revised accordingly.
Appendix 5: Summary of Changes	• Added Appendix 5 due to Amendment 1 changes.
Throughout	• Changed study week numbers accordingly to reflect the change in End of Study Visit week. • Replaced any reference to the pre-filled syringe of EYLEA® (aflibercept) to just EYLEA® (aflibercept). • Miscellaneous typographical and formatting issues were corrected, and some hyperlinks were fixed and/or added.

The following changes were made to Protocol EYP-1901-201 as Amendment 2 (v2.1):

SECTION(S)	CHANGE/RATIONALE
Synopsis Section 4.2	• Exclusion criterion #7 (regarding intraretinal cystic fluid at Screening) was slightly changed by defining the abbreviations (IRF and ELM) and removing them as they are used no where else in the protocol.
Table 1–1 List of Abbreviations	• Removed ELM and IRF from the table.
Section 5.1.6 Section 5.1.8	• Updated these sections to reflect changes made in Table 5–1 with Amendment 1 regarding aflibercept and sham dosing continuing through the new End of Study visit at Week 56.
Throughout	• Miscellaneous typographical and formatting issues were corrected, and some hyperlinks were fixed and/or added.

The following changes were made to Protocol EYP-1901-201 as Amendment 3 (v3.0):

SECTION(S)	CHANGE/RATIONALE
Synopsis Section 3.2	• Parties unmasked after last subject completes Week 32 updated to only the Sponsor/CRO will be unmasked at Week 32 to conduct endpoint analysis.

The following changes were made to Protocol EYP-1901-201 as Amendment 4 (v4.0):

SECTION(S)	CHANGE/RATIONALE
Synopsis Section 4.1	• Modified inclusion criterion #2 to include subjects who onset of disease in the past 4 years since the Screening Visit instead of 9 months in order to expand the subject population.
Synopsis Section 4.1	• Added faricimab to inclusion criterion #4.
Synopsis Section 4.2	• Modified exclusion criterion #6 to adjust the CST in the study eye at Screening [Day 1] from >400 µm to >350 µm to allow enrollment of subjects with less excess fluid into the study.
Section 4.2	• Corrected typos in the exclusion criteria #24 to match the correct BCVA reading using ETDRS charts listed in the protocol synopsis.
Section 4.3	• As requested by the Central IRB, the pregnancy and contraception section was updated to align with the contraception requirements for aflibercept.
Synopsis Section 3.1 Section 5.1.4	• Added the timing window for EYP-1901 and sham administration after receiving aflibercept.
Section 7.1.1	• Ocular AEs was updated to define moderate or severe as Grade 2 and 3 for consistency with the AE grading descriptions in Section 7.1.5 and Appendix 4.
Table 5–1 Schedule of Assessments Appendix 2	• Added the window of time for IOP measurement following study treatment administration in Table 5–1 (footnote "e) and in Appendix 2.
Throughout	• Miscellaneous typographical and formatting issues were corrected, and some hyperlinks were fixed and/or added.

The following changes were made to Protocol EYP-1901-201 as Amendment 5 (v5.0):

SECTION(S)	CHANGE/RATIONALE
Synopsis Section 3.1.1 Section 4.1	• Changed the BCVA from 20/25 (80 letters) to 20/20 (85 letters) in inclusion criterion #6 to include subjects in the study who may demonstrate visual stability.
Synopsis Section 3.1 Section 11.3.4	• Modified the number of study sites from 50 to approximately 70.
Section 4	• Clarified the details regarding subject eligibility to assist Investigators when making decisions to reassess and rescreen subjects during the Screening period.
Synopsis Section 4.2	• Added "in the study eye" to exclusion criterion #39.
Synopsis Section 4.1	• Modified inclusion criterion #2 to include subjects who had an onset of wAMD disease that began at any time prior the Screening Visit instead of 4 years to expand the subject population.
Synopsis Section 4.2	• Changed the RPED thickness from > 300 µm to > 400 µm in exclusion criterion #11 to include subjects in the study with larger RPEDs.
Synopsis Section 2 Section 6.6.4	• Modified the rescue criteria to specify that it was specific to the study eye.
Section 7	• Removed the drug safety committee and added details regarding the Sponsor conducting ongoing medical safety reviews throughout the study.
Throughout	• Miscellaneous typographical and formatting issues were corrected, and some hyperlinks were fixed and/or added.

The following changes were made to Protocol EYP-1901-201 as Amendment 6 (v6.0):

SECTION(S)	CHANGE/RATIONALE
Personal Contact Information	• Changed the Drug Safety Physician from PPD to PPD
Synopsis, Objectives Section 2	• Changed the objective regarding the ocular exposure to EYP-1901 measured through aqueous levels up to Week 32 instead of up to Week 56. The Sponsor has collected the adequate number of aqueous humor samples at Week 32.
Synopsis Section 3.1.1	• Clarified that if during an unscheduled visit or if posterior inflammation is present in the study eye, CFP and OCT of the study eye **should** be collected at a minimum.
Table 5–1 Section 5.1.6 Section 5.1.7 Section 5.1.8	• Removed the aqueous humor PK collection from Weeks 44 and 56 because the Sponsor has collected the adequate number of aqueous humor samples.
Section 1.1	• Changed the Sponsor of Yutiq® from EyePoint Pharmaceuticals, Inc to Alimera Sciences.
Section 3.3	• Changed the status of the Phase 1 DAVIO study from "ongoing" to "completed".

SECTION(S)	CHANGE/RATIONALE
Personal Contact Information	• Changed the Drug Safety Physician from PPD to PPD.
Throughout	• Miscellaneous typographical and formatting issues were corrected, and some hyperlinks were fixed and/or added.