EYP-1901
(VOROLANIB INTRAVITREAL INSERT)

PROTOCOL EYP-1901-204

A Phase 2, Multicenter, Prospective, Double-masked, Parallel Study of EYP-1901, a Tyrosine Kinase Inhibitor (TKI), compared to Sham for the Improvement of Moderately Severe to Severe Nonproliferative Diabetic Retinopathy (NPDR)

IND Number	146448
Sponsor:	EyePoint Pharmaceuticals, Inc. 480 Pleasant Street Watertown, MA 02472 USA
Version:	Version 3.0: 31 March 2023 Version 2.0: 10 May 2022 Original Protocol: 26 Feb 2022

PROTOCOL APPROVAL PAGE

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Date: 31 March 2023

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

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	[n/a]	[n/a]
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, Pharmacovigilance 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, Double-masked, Parallel Study of EYP-1901, a Tyrosine Kinase Inhibitor (TKI), compared to Sham for the Improvement of Moderately Severe to Severe Nonproliferative Diabetic Retinopathy (NPDR)

Protocol Number: EYP-1901-204	**Phase of Development:** 2

Study Sites: Approximately 30 sites in the US

Studied Period: Up to 48 weeks of follow-up

Objectives: The primary objective is to assess the efficacy of EYP-1901 compared to sham treatment in the improvement of moderately severe to severe nonproliferative diabetic retinopathy (NPDR).

The secondary objectives are:

- To characterize the safety of EYP-1901 in subjects with moderately severe to severe NPDR.
- To determine if EYP-1901 will prevent the worsening of diabetic retinopathy and reduce the incidence of diabetic macular edema (DME).
- To evaluate the need for additional standard of care intervention due to ocular diabetic complications.
- To determine the anatomic effects of EYP-1901 in subjects with moderately severe to severe NPDR.
- To determine the systemic exposure to vorolanib and X-297, its main metabolite, measured through plasma levels up to Week 48.

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

- Subjects with NPDR who meet the study eligibility criteria will be randomly assigned to EYP-1901 2060 µg dose, EYP-1901 3090 µg dose, or sham intravitreal (IVT) injection.
- Follow-up examinations will be conducted at Week 4, 12, 24, 36, and 48 following study drug administration.

Number of Subjects (planned): Approximately 60 subjects (20 subjects per treatment arm).

Inclusion Criteria:

1. Men or women ≥18 years of age with type 1 or 2 diabetes mellitus. Participants must have a hemoglobin A1c (HbA1c) ≤12% (as confirmed by laboratory assessments obtained at the Screening Visit or by a documented laboratory report dated within 60 days prior to the Screening Visit).

2. Study eye with moderately severe to severe NPDR (based on the Diabetic Retinopathy Severity Scale [DRSS] levels 47 or 53), using standard 4-widefield digital stereoscopic fundus photographs confirmed by the central reading center (CRC), in whom pan-retinal photocoagulation (PRP) and anti-vascular endothelial growth factor (anti-VEGF) injections can be safely deferred for at least 6 months per the Investigator.
3. Best corrected visual acuity (BCVA) using Early Treatment Diabetic Retinopathy Study (ETDRS) letter score in the study eye of ≥69 letters (approximate Snellen equivalent of 20/40 or better).
4. 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.
5. Willingness and ability to comply with all scheduled visits, restrictions, and assessments.
6. For women of childbearing potential, or men with female partners of childbearing potential, agreement to the use of an appropriate form of contraception for the duration of the study.

Exclusion Criteria:

1. Presence of any active center involved-diabetic macular edema (CI-DME) in the study eye as determined by the Investigator on clinical examination, or within the central subfield thickness (CST) of the study eye as determined by spectral-domain – optical coherence tomography (SD-OCT) evaluated by the CRC, with a CST threshold greater than 320 microns.
2. Evidence of retinal neovascularization on clinical examination or wide-field fluorescein angiography (FA).
3. Any evidence or documented history of prior focal or grid laser photocoagulation or any PRP in the study eye in the last 12 months.
4. Any evidence of optic nerve pallor on clinical examination in the study eye as determined by the Investigator.
5. Any evidence of high-risk characteristics typically associated with vision loss in the study eye as determined by the Investigator.
6. Any evidence of new vascularization anywhere (neovascularization of the iris [NVI], neovascularization of the angle [NVA], neovascularization everywhere [NVE], neovascularization of the disc [NVD]) on clinical examination as per the Investigator, or imaging evaluated by the CRC, in the study eye.
7. Any prior systemic anti-VEGF treatment in the past 12 months.
8. Any prior IVT anti-VEGF treatment in the past 12 months.
9. Any documentation of more than 4 prior anti-VEGF IVT injections in the study eye.
10. Any concurrent intraocular condition in the study eye (eg, 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.
11. History of prior vitrectomy surgery in study eye.
12. Historical or active intraocular inflammation (grade trace or above) in the study eye, other than expected findings from routine cataract surgery.
13. History of vitreous hemorrhage in the study eye within 12 weeks prior to the Screening Visit.

14. History of rhegmatogenous retinal detachment or treatment for retinal detachment or macular hole (stage 3 or 4) in the study eye.
15. Aphakia or pseudophakia with the absence of the posterior capsule in the study eye (YAG capsulotomy is permitted).
16. Spherical equivalent of the refractive error in the study eye demonstrating >8 diopters of myopia. 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.
17. Intraocular surgery (including cataract surgery) in the study eye within 12 weeks prior to the Screening Visit.
18. 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 two or more classes of antiglaucoma medication) and any such condition which the Investigator feels may require a glaucoma filtering surgery while in the study.
19. History of glaucoma-filtering surgery, tube shunts, or microinvasive glaucoma surgery in the study eye.
20. History of corneal transplant in the study eye.
21. Any prior intraocular corticosteroid injection in the study eye in the past 12 months.
22. Current anterior segment neovascularization (ASNV), vitreous hemorrhage, or tractional retinal detachment visible at the screening assessments in the study eye.
23. 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.
24. Prior participation in a clinical trial involving investigational ocular gene therapy for either eye.
25. History of idiopathic or autoimmune-associated uveitis in either eye.
26. Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.
27. 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.
28. 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.
29. 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.
30. Serious non-healing wound, ulcer, or bone fracture.
31. 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.
32. Current treatment for any active systemic infection.
33. Use of oral corticosteroids (prednisone >10 mg/day or equivalent) within 30 days prior to the Screening Visit.

34. 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 in the past 2 years.
35. 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.
36. History of allergy to fluorescein, not amenable to treatment.
37. Inability to obtain fundus photographs, wide-field FA, fundus autofluorescence, or SD-OCT images of sufficient quality to be analyzed and graded by the CRC.
38. 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.
39. 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).
40. Use of anti-mitotic or anti-metabolite therapy within 30 days or 5 elimination half-lives of the Screening Visit, whichever is longer.
41. Intolerance, contraindication, or hypersensitivity to topical anesthetics, dyes, povidone iodine, mydriatic medications, or any of the ingredients of the EYP-1901 insert.
42. Requirement for continuous use of any protocol-prohibited medications or treatments.
43. 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 the EYP-1901 intravitreal insert (the test article) in the designated study eye.

Control: Sham IVT injection

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 insert is 8 mm long and is designed to deliver vorolanib into the vitreous humor at two different doses for at least 9 months. Single or multiple inserts will be administered to the study eye at Day 1 by injection through the pars plana using a pre-loaded applicator with a 22-gauge needle. Two of the following doses will be selected based upon ongoing Phase 1 studies:

- 2060 µg dose, 2 inserts, 22-gauge needle
- 3090 µg dose; 3 inserts, 22-gauge needle

Designation of Study Eye: For subjects with unilateral NPDR, the affected eye will be designated as the study eye; for subjects with bilateral NPDR, the study eye will be the more severely affected eye meeting the inclusion/exclusion criteria, ie, the eye having the worse DRSS 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. The fellow eye will receive treatment as needed and according to the Investigator's judgment.

Study Procedures: Assessments will include the ETDRS-DRSS score on 4-widefield digital stereoscopic fundus photography, BCVA by ETDRS, anterior/posterior segment ocular examination, intraocular pressure (IOP), wide-field FA, color fundus photography (CFP), ocular and non-ocular

treatment-emergent adverse events (TEAEs), clinical laboratory evaluations (HbA1c, hematology, serum chemistry, coagulation, and urinalysis), bioanalytical testing for plasma levels of vorolanib and X-297, its main metabolite, heart rate and blood pressure measurements, SD-OCT, and, at study sites where equipment is available, OCT-angiography (OCT-A). Photographs will be sent to the CRC for analysis.

Follow-up Visits: Following injection on Study Day 1, subjects will return at Weeks 4, 12, 24, 36, and 48 (see details in attached Schedule of Study Procedures and Assessments).

Masking: Except for the Investigators administering the study treatments, masking will be maintained for both subjects and the Investigators conducting the study assessments. Sham IVT injections will be used during the study to maintain masking of investigational EYP-1901 therapy for study subjects. Only the Sponsor/CRO will be unmasked after the last subject completes the Week 36 visit to conduct endpoint analysis.

Criteria for Evaluation in the Study Eye:

Primary Endpoint:

- Percentage of subjects improving ≥2 steps from baseline in the DRSS score at Week 36 in each dose level vs. sham.

The DRSS may be used to describe overall retinopathy severity as well as the change in severity over time. Severity ranges from level 10 (DR absent) to level 85 (advanced proliferative DR: posterior fundus obscured, or center of macula detached). Here, DRSS describes severity level 47 (moderately severe NPDR) and level 53 (severe NPDR) at Week 36 from baseline.

Secondary Endpoints:

- Percentage of subjects improving ≥2 steps from baseline in the DRSS score at Weeks 24 and 48 in each dose level vs. sham.
- Percentage of subjects improving ≥2-steps or ≥3-steps over time in DRSS from baseline.
- Percentage of subjects worsening ≥2-steps or ≥3-steps over time in DRSS from baseline.
- Percentage of subjects who developed a vision-threatening complication due to diabetic retinopathy at Weeks 24, 36, and 48.
- Percentage of subjects who developed CI-DME at Weeks 24, 36, and 48.
- Time to develop any neovascular vision threatening complication (PDR/ASNV) through Weeks 24, 36, and 48.
- Time to develop CI-DME through Weeks 24, 36, and 48.
- Percentage of subjects who received anti-VEGF or additional standard of care intervention due to ocular diabetic complications at Weeks 24, 36 and 48.
- Percentage of subjects who received PRP, inclusive of subjects undergoing vitrectomy with endolaser, at Weeks 24, 36, and 48.
- Area Under the Curve (AUC) for change from baseline in BCVA at Weeks 24, 36, and 48.
- Systemic exposures to vorolanib and X-297, its main metabolite, measured through plasma levels up to Weeks 24, 36, and 48.
- Rates of ocular (study eye and fellow eye) and non-ocular TEAEs at Weeks 24, 36, and 48.

Statistical Methods:

Sample Size:

The objectives of the study are to provide efficacy and safety data in a prospective, randomized, double-masked, controlled trial. However, the study is not formally powered to perform statistical hypothesis testing between each EYP-1901 arm versus sham IVT injection. Approximately 60 subjects will be randomized at 1:1:1 ratio to each of three treatment arms (20 per treatment arm).

Efficacy and Safety Analyses:

Descriptive statistics by treatment arm will be provided for all TEAEs, DRSS scores, BCVA and imaging endpoints, and plasma pharmacokinetic data. Frequency counts and percentage of subjects will be provided by MedDRA system organ class (SOC) and preferred term (PT) by dose cohort. 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
ASNV	Anterior segment neovascularization
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BCVA	Best corrected visual acuity
CFP	Color fundus photography
CFR	(US) Code of Federal Regulations
CI-DME	Center involved-diabetic macular edema
CPR	Cardiopulmonary resuscitation
CRA	Clinical Research Associate
CRC	Central reading center
CRO	Contract Research Organization
CST	Central subfield thickness
CTCAE	(National Cancer Institute's) Common Toxicity Criteria for Adverse Events
DME	Diabetic macular edema
DRSS	Diabetic Retinopathy Severity Scale
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
FDA	Food and Drug Administration
GCP	Good Clinical Practice (guidelines)
HbA1c	Hemoglobin A1c (reported in %)
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFU	Instructions for Use
IND	Investigational New Drug application
IOP	Intraocular pressure
IRB	Institutional Review Board
ITT	Intent-to-treat
IVT	Intravitreal
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
NPDR	Nonproliferative Diabetic Retinopathy
NVA	Neovascularization of the angle
NVD	Neovascularization of the disc
NVE	Neovascularization everywhere
NVI	Neovascularization of the iris
NYHA	New York Hospital Association
OCT-A	Optical coherence tomography - angiography

Abbreviation or Specialist Term	Explanation
OTC	Over-the-counter
PDGF	Platelet-derived growth factor
PK	Pharmacokinetic
PRP	Pan-retinal photocoagulation
PT	Preferred term
SADR	Serious Adverse Drug Reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD-OCT	Spectral-domain – optical coherence tomography
SOC	System Organ Class
SOP	Standard Operating Procedure
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 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 the Durasert® platform, a proprietary sustained delivery technology used in FDA-approved intraocular products indicated for the treatment of posterior segment uveitis, such as Retisert® (Bausch & Lomb, Inc., USA) and Yutiq® (EyePoint Pharmaceuticals, Inc., 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 daily into the ocular vitreous chamber for the treatment of wet age-related macular degeneration (wAMD) and nonproliferative diabetic retinopathy (NPDR).

1.2 Overview of NPDR

Diabetic retinopathy is the leading cause of new blindness in the US, with a prevalence rate in adults with diabetes of approximately 28.5% (https://emedicine.medscape.com/article/1225122-overview). The global impact of DR-related vision complications is expected to rise given the increasing rates of diabetes across the US and other developed countries. As ocular manifestations often precede other systemic complications of diabetes mellitus, eye care specialists play a critical role in the prevention, diagnosis, and management of diabetic eye disease.

There are several stages of DR, ranging from mild nonproliferative disease to severe proliferative disease. While the most common early clinically manifestations of NPDR include formation of microaneurysms and intraretinal hemorrhages, these patients do not present with any symptoms. Progressing in stage, further damage can be observed such as intraretinal microvascular abnormalities, cotton wool spots, increased numbers of hemorrhages, and venous caliber abnormalities. At any stage in the course of the disease, increased vasopermeability results in retinal thickening (edema) and/or exudates that may lead to a loss in central vision. The proliferative diabetic retinopathy (PDR) stage results from closure of arterioles and venules with secondary proliferation of new vessels on the retina, optic disc, or anterior segment. Common complications of DR that puts the patient's vision at risk and requires either urgent medical or surgical intervention include center involved-diabetic macular edema (CI-DME), tractional retinal detachments, epiretinal membranes, and vitreous hemorrhage. The risk of these complications usually increases as the severity of DR increases, although DME can be present at any stage of DR (Aiello et al. 1994). The link between diabetic ischemia and subsequent proliferation of angiogenic factors including VEGF has been established.

Preventing the conversion to PDR and the associated vision threatening complications has the potential to improve the quality of a patient lives for decades. The ability to minimize sight-threatening diabetic complications in the working-age population could have significant impact on public health.

While both ranibizumab (LUCENTIS®) and aflibercept (EYLEA®) have demonstrated that intravitreal (IVT) anti-VEGF therapy can effectively regress the severity of DR, the use of these agents in clinical practice remains limited due to the need for regular treatment and visits to achieve the desired outcomes (LUCENTIS® and EYLEA® prescribing information). EYP-1901 could potentially provide long-term treatment to patients.

For this Phase 2 clinical study, participants with moderately severe to severe NPDR without CI-DME at baseline will be enrolled. This represents a population that is often observed without treatment in clinical practice until signs of high-risk proliferative disease are present. These patients are at significant risk of progressing to more serious vision threatening stages of DR. Therefore, this population of patients has the potential to benefit from EYP-1901 long lasting treatment.

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 to prevent the progression to more serious vision threatening stages of DR. 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 both investigated in nonclinical efficacy models and in nonclinical safety and pharmacokinetic studies. 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 third clinical investigational study of EYP-1901 (vorolanib intravitreal insert); a previous Phase 1 dose-escalation study (ie, the DAVIO trial) in patients with wAMD was initiated in Jan 2021 and a Phase 2 trial in patients with wAMD will be initiated in mid-2022. Interim safety and efficacy analyses conducted upon completion of Week 24 in the DAVIO study provided support for initiation of the present Phase 2 study.

For X-82 (oral vorolanib), two previous studies were conducted in wAMD (Jackson et al. 2017; Cohen et al. 2021). For additional details on the clinical experience from previous EYP-1901 and X-82 studies please refer to the current EYP-1901 IB.

2 STUDY OBJECTIVES

The primary objective is to assess the efficacy of EYP-1901 compared to sham treatment in the improvement of moderately severe to severe NPDR.

The secondary objectives are:

- To characterize the safety of EYP-1901 in subjects with moderately severe to severe NPDR.

- To determine if EYP-1901 will prevent the worsening of diabetic retinopathy and reduce the incidence of DME.
- To evaluate the need for additional standard of care intervention due to ocular diabetic complications.
- To determine the anatomic effects of EYP-1901 in subjects with moderately severe to severe NPDR.
- To determine the systemic exposure to vorolanib and X-297, its main metabolite, measured through plasma levels up to Week 48.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

This is a prospective, randomized, double-masked, multicenter study evaluating the ocular efficacy and safety of two doses of the EYP-1901 intravitreal insert compared to sham in adult subjects with NPDR. Up to 60 subjects will be randomized on a 1:1:1 basis to three different treatment arms (2060 µg EYP-1901, 3090 µg EYP-1901, or sham IVT injection) across approximately 30 sites in the US, such that each treatment arm will include up to 20 subjects. All subjects, irrespective of treatment arm, will receive an IVT injection on Day 1 in the designated study eye.

Following injection on Day 1, subjects will return at Weeks 4, 12, 24, and 48 following study drug administration. The Schedule of Assessments is presented in Table 5–1.

3.1.1 General Study Methods

For subjects with unilateral NPDR, the affected eye will be designated as the study eye; for subjects with bilateral NPDR, the study eye will be the more severely affected eye meeting the inclusion/exclusion criteria, ie, the eye having the worse Diabetic Retinopathy Severity Scale (DRSS) score 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. The fellow eye will receive treatment as needed and according to the Investigator's judgment.

Subjects ≥18 years of age with type 1 or 2 diabetes mellitus (documented hemoglobin A1c [HbA1c] ≤12%) and an active diagnosis of moderately severe to severe NPDR (based on DRSS levels 47 or 53) in whom pan-retinal photocoagulation (PRP) and anti-VEGF injections can be safely deferred for at least 6 months as per the Investigator, and who satisfy all other protocol eligibility criteria up until dosing on Day 1, will be enrolled and receive the assigned study treatment.

Study procedures will include: ETDRS-DRSS score on 4-widefield digital stereoscopic fundus photography, best corrected visual acuity (BCVA) by ETDRS, anterior/posterior segment ocular examination, intraocular pressure (IOP), wide-field fluorescein angiography (FA), color fundus photography (CFP), ocular and non-ocular treatment-emergent adverse events (TEAEs), clinical laboratory evaluations (HbA1c, hematology, serum chemistry, coagulation, and urinalysis), bioanalytical testing for plasma levels of vorolanib and X-297, its main metabolite, heart rate and blood pressure measurements, spectral-domain – optical coherence tomography (SD-OCT),

and, at study sites where equipment is available, OCT-angiography (OCT-A). Photographs will be sent to the central reading center (CRC) for analysis.

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 investigational EYP-1901 therapy for study subjects. Only the Sponsor/CRO will be unmasked after the last subject completes the Week 36 visit 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.

3.2.1 Emergency Unmasking

Unmasking a subject's treatment to the assessing Investigator should only be done in emergency situations for reasons of subject safety.

At the initiation of the study, the clinical sites will receive instructions for unmasking a subject.

In the event that an emergency unmasking is required, the assessing Investigator/medically qualified designee has the authority to unmask a subject's treatment using IXRS, or its back-up system if IXRS is not functioning. If possible, the assessing Investigator/medically qualified designee should contact the Medical Monitor or designee before breaking the mask.

When the masked treatment code is broken, the date and time of unmasking, name of person doing the unmasking, and the reason for unmasking must be fully documented in the source documentation.

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

The prospective, randomized, double-masked study with a sham IVT injection control group is an acceptable design for the evaluation of comparative efficacy and safety of two doses of EYP-1901.

The two doses (2060 µg and 3090 µg) chosen for EYP-1901 were based on the safety profile through Week 36 in the ongoing Phase 1 DAVIO study (see details in Section 1.5).

3.4 Duration of Study

Total study participation will be approximately 52 weeks (including the Screening period). After the initial Screening Visit, subjects may have between 5 and 30 days to be enrolled, at which point the study treatments/control will be administered 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 Day 1 study treatment dosing, the follow-up period will be through 48 weeks (with visit windows of ±7 days starting at Week 4). Eligible subjects who are enrolled in this study will be seen for the scheduled study visits over approximately 12 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 48 visit (End of Study Visit).

3.5 Recording of Injection Procedure

The injection procedure of EYP-1901 or sham 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 20 subjects each will be enrolled to assess the efficacy and safety of 2060 µg or 3090 µg EYP-1901 intravitreal insert compared to sham IVT injection.

Subjects will be enrolled in the study only if they meet all the following eligibility criteria; continued eligibility will be assessed again at treatment randomization on Day 1. 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. Men or women ≥18 years of age with type 1 or 2 diabetes mellitus. Participants must have a HbA1c ≤12% (as confirmed by laboratory assessments obtained at the Screening Visit or by a documented laboratory report dated within 60 days prior to the Screening Visit).
2. Study eye with moderately severe to severe NPDR (based on the DRSS levels 47 or 53), using standard 4-widefield digital stereoscopic fundus photographs confirmed by the CRC, in whom PRP and anti-VEGF injections can be safely deferred for at least 6 months per the Investigator.
3. Best corrected visual acuity (BCVA) using Early Treatment Diabetic Retinopathy Study (ETDRS) letter score in the study eye of ≥69 letters (approximate Snellen equivalent of 20/40 or better).
4. 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.
5. Willingness and ability to comply with all scheduled visits, restrictions, and assessments.
6. For women of childbearing potential, or men with female partners of childbearing potential, agreement to the use of an appropriate form of contraception for the duration of the study.

4.2 Exclusion Criteria

1. Presence of any active CI-DME in the study eye as determined by the Investigator on clinical examination, or within the central subfield thickness (CST) of the study eye as determined by SD-OCT evaluated by the CRC, with a CST threshold greater than 320 microns.
2. Evidence of retinal neovascularization on clinical examination or wide-field FA.
3. Any evidence or documented history of prior focal or grid laser photocoagulation or any PRP in the study eye in the last 12 months.
4. Any evidence of optic nerve pallor on clinical examination in the study eye as determined by the Investigator.
5. Any evidence of high-risk characteristics typically associated with vision loss in the study eye as determined by the Investigator.
6. Any evidence of new vascularization anywhere (neovascularization of the iris [NVI], neovascularization of the angle [NVA], neovascularization everywhere [NVE], neovascularization of the disc [NVD]) on clinical examination as per the Investigator, or imaging evaluated by the CRC, in the study eye.
7. Any prior systemic anti-VEGF treatment in the past 12 months.
8. Any prior IVT anti-VEGF treatment in the past 12 months.
9. Any documentation of more than 4 prior anti-VEGF IVT injections in the study eye.
10. Any concurrent intraocular condition in the study eye (eg, 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.
11. History of prior vitrectomy surgery in study eye.
12. Historical or active intraocular inflammation (grade trace or above) in the study eye, other than expected findings from routine cataract surgery.
13. History of vitreous hemorrhage in the study eye within 12 weeks prior to the Screening Visit.
14. History of rhegmatogenous retinal detachment or treatment for retinal detachment or macular hole (stage 3 or 4) in the study eye.
15. Aphakia or pseudophakia with the absence of the posterior capsule in the study eye (YAG capsulotomy is permitted).
16. Spherical equivalent of the refractive error in the study eye demonstrating >8 diopters of myopia. 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.
17. Intraocular surgery (including cataract surgery) in the study eye within 12 weeks prior to the Screening Visit.

18. Uncontrolled ocular hypertension or glaucoma in the study eye (defined as IOP >25 mmHg or a cup to disc ratio ≥0.8, despite treatment with two or more classes of antiglaucoma medication) and any such condition which the Investigator feels may require a glaucoma filtering surgery while in the study.
19. History of glaucoma-filtering surgery, tube shunts, or microinvasive glaucoma surgery in the study eye.
20. History of corneal transplant in the study eye.
21. Any prior intraocular corticosteroid injection in the study eye in the past 12 months.
22. Current anterior segment neovascularization (ASNV), vitreous hemorrhage, or tractional retinal detachment visible at the screening assessments in the study eye.
23. 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.
24. Prior participation in a clinical trial involving investigational ocular gene therapy for either eye.
25. History of idiopathic or autoimmune-associated uveitis in either eye.
26. Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.
27. 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.
28. 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.
29. 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.
30. Serious non-healing wound, ulcer, or bone fracture.
31. 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.
32. Current treatment for any active systemic infection.
33. Use of oral corticosteroids (prednisone >10 mg/day or equivalent) within 30 days prior to the Screening Visit.
34. 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 in the past 2 years.

35. 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.
36. History of allergy to fluorescein, not amenable to treatment.
37. Inability to obtain fundus photographs, wide-field FA, fundus autofluorescence, or SD-OCT images of sufficient quality to be analyzed and graded by the CRC.
38. 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.
39. 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).
40. Use of anti-mitotic or anti-metabolite therapy within 30 days or 5 elimination half-lives of the Screening Visit, whichever is longer.
41. Intolerance, contraindication, or hypersensitivity to topical anesthetics, dyes, povidone iodine, mydriatic medications, or any of the ingredients of the EYP-1901 insert.
42. Requirement for continuous use of any protocol-prohibited medications or treatments.
43. 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.

4.3 Pregnancy and Contraception

Women of childbearing potential must be practicing and willing to continue using a highly effective method of birth control during the course of the study, such as: oral contraceptive pill (eg, Ortho Tri-Cyclen®); injection (eg, Depo Provera®); implant (eg, Norplant®); patch (eg, Ortho Evra Patch®); vaginal ring (eg, NuvaRing®); intrauterine coil (eg, Mirena® coil); intrauterine device (IUD) with or without hormones; a barrier method (eg, latex condom, diaphragm, or cap) used **with an additional form of contraception** (ie, **two methods** [eg, sponge, spermicide, hormonal contraceptive pill, or injection]); or complete abstinence. 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 (or if complete abstinence is being followed)
- 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 of EYP-1901, 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 PPD 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 and 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:

- Resolution
- Stabilization or severity to the National Cancer Institute's Common Toxicity Criteria for Adverse Events (CTCAE) Grade 1/mild
- Returned to baseline status
- Subject is lost to follow-up
- 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 (eg, 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 at all visits as described in the Schedule of Study Procedures and Assessments (Table 5–1) unless otherwise indicated.

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).

Wide-Field 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).

ETDRS-DRSS: The CFP images will be assessed by the CRC to determine the ETDRS-DRSS score on 4-widefield digital stereoscopic fundus photography for study eligibility (specifically Inclusion Criterion #2) and for the primary efficacy endpoint (ie, percentage of subjects improving ≥2 steps from baseline in the DRSS score at Week 36 in each dose level vs. sham). The DRSS may be used to describe overall retinopathy severity as well as the change in severity over time. Severity ranges from level 10 (DR absent) to level 85 (advanced proliferative DR: posterior fundus obscured, or center of macula detached). Here, DRSS describes severity level 47 (moderately severe NPDR) and level 53 (severe NPDR) at Week 36 from baseline.

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.

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. Starting at Week 4, study visits should be conducted within ±7 days for all scheduled visits.

Table 5–1: Schedule of Study Procedures and Assessments, Study EYP-1901-204

	Screening	Study Treatment and Follow-Up						
	Days -30 to -5	Day 1	Week 4	Week 12	Week 24	Week 36	Week 48	ET[a]
Time Window (in days)			±7	±7	±7	±7	±7	
Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
Randomization		X						
Demographics	X							
Vital Signs[b]	X	X	X	X	X	X	X	X
Standard 12-lead ECG	X						X	X
Medical and Medication History	X							
Pre-Injection IOP (bilateral)		X						
Ocular Examination (bilateral)[c]	X	X	X	X	X	X	X	X
Study Drug/Sham Dosing[d] (study eye only)		X						
Post-Injection/Sham injection IOP[e]		X						
ETDRS BCVA (bilateral)	X	X	X	X	X	X	X	X
Color Fundus Photography (bilateral)[f]	X	X	X	X	X	X	X	X
Wide-Field FA (bilateral)	X				X	X	X	X
SD-OCT Assessment (bilateral)	X	X	X	X	X	X	X	X
SD-OCTA Assessment (bilateral)[g]	X				X		X	X
Clinical Laboratory Evaluations[h]	X[i]			X	X	X	X	X
Urine Pregnancy Test[j]	X						X	X
Blood sampling for PK[k]		X		X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Events[l]	X	X	X	X	X	X	X	X

BCVA = best corrected visual acuity; CFP = color fundus photography; DRSS = Diabetic Retinopathy Severity Scale; ECG = electrocardiogram; ETDRS = Early Treatment Diabetic Retinopathy Study; ET = early termination; FA = fluorescein angiography; HbA1c = hemoglobin A1c; IOP = intraocular pressure; PK = pharmacokinetic; SD-OCT = spectral domain – optical coherence tomography; SD-OCTA = spectral-domain – optical coherence tomography angiography

Note During any unscheduled visit or if posterior inflammation is present in the study eye, CFP, SD-OCT, and wide field FA of the study eye should be collected at a minimum.

(table footnotes on next page)

Footnotes for Table 5-1:

a. Subjects who terminate the study prior to the Week 48 (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, including dilated ophthalmoscopy, IOP, and slit lamp biomicroscopy (see Appendix 2).

d. Check central retinal artery perfusion following study injection.

e. At Day 1: measure IOP at 10 (+/- 5) and 60 (+/- 10) minutes following the EYP-1901 dose/sham injection. If IOP measurements at any study time points are 30 mmHg or higher, two additional measurements should be performed and IOP recorded as a mean of three measurements.

f. All CFP images will be assessed by the CRC to determine the ETDRS-DRSS scores.

g. 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.

h. Clinical laboratory testing will include HbA1c, hematology, serum chemistry, coagulation, and urinalysis evaluations (refer to the study Laboratory Manual).

i. Documented HbA1c test results dated 60 days prior to the Screening Visit will be accepted.

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

k. Pharmacokinetic analyses of vorolanib and X-297, its main metabolite, will be performed on blood plasma samples.

l. 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 -30 to Day -5 (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. 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)
- Ocular examination – dilated ophthalmoscopy, IOP, and slit lamp biomicroscopy (Appendix 2)
- CFP
- Wide-field FA
- SD-OCT assessment
- 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)
- Documented HbA1c ≤12% for Inclusion Criterion #1 (confirmed by laboratory evaluation at the Screening Visit or by a documented laboratory report dated within 60 days prior to the Screening Visit).
- Urine pregnancy test (females of childbearing potential only)
- 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 (Study Treatment)

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 EYP-1901 or sham IVT injection in the designated study eye on Day 1.

For subjects with unilateral NPDR, the affected eye will be designated as the study eye; for subjects with bilateral NPDR, the study eye will be the more severely affected eye meeting the inclusion/exclusion criteria, ie, the eye having the worse DRSS 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. The fellow eye will receive treatment as needed and according to the Investigator's judgment.

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

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

Non-ocular procedures to be performed:

- Vital sign measurements (Section 7.3)
- Blood sampling for PK analysis (Section 9)
- 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, SD-OCT, and wide-field FA of the study eye should be collected at a minimum.

5.1.3 Week 4 (±7 days)

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)
- Ocular examination – dilated ophthalmoscopy, IOP, and slit lamp biomicroscopy (Appendix 2)
- CFP
- SD-OCT assessment

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 12 (±7 days)

The following procedures will be completed during the Week 12 visit (Table 5–1).

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

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

Non-ocular procedures to be performed:

- Vital sign measurements (Section 7.3)
- Collect blood and urine samples for clinical laboratory evaluations (including HbA1c) (Section 7.2)
- Blood sampling for PK analysis (Section 9)
- Use of concomitant medications (Section 7.5)
- Adverse events (Section 7.1)

5.1.5 Week 24 (±7 days)

The following procedures will be completed during the Week 24 visit (Table 5–1).

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

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

Non-ocular procedures to be performed:

- Vital sign measurements (Section 7.3)
- Collect blood and urine samples for clinical laboratory evaluations (including HbA1c) (Section 7.2)
- Blood sampling for PK analysis (Section 9)
- Use of concomitant medications (Section 7.5)
- Adverse events (Section 7.1)

5.1.6 Week 36 (±7 days)

The following procedures will be completed during the Week 36 visit (Table 5–1).

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

- ETDRS BCVA (Appendix 1)
- Ocular examination – dilated ophthalmoscopy, IOP, and slit lamp biomicroscopy (Appendix 2)
- CFP
- Wide-field FA
- SD-OCT assessment

Non-ocular procedures to be performed:

- Vital sign measurements (Section 7.3)
- Collect blood and urine samples for clinical laboratory evaluations (including HbA1c) (Section 7.2)
- Blood sampling for PK analysis (Section 9)
- Use of concomitant medications (Section 7.5)
- Adverse events (Section 7.1)

5.1.7 Week 48 (±7 days, End of Study) and Early Termination Visit

Subjects who terminate the study prior to the Week 48 visit should undergo all procedures noted for the Early Termination Visit in Table 5–1.

The following procedures will be completed during the Week 48 or ET visits (Table 5–1).

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

- ETDRS BCVA (Appendix 1)
- Ocular examination – dilated ophthalmoscopy, IOP, and slit lamp biomicroscopy (Appendix 2)
- CFP
- Wide-field FA

- SD-OCT assessment
- 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 (including HbA1c) (Section 7.2)
- Urine pregnancy test (females of childbearing potential only)
- Blood sampling for PK analysis (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 (eg, ETDRS-DRSS, BCVA by ETDRS, slit lamp biomicroscopy, dilated ophthalmoscopy, IOP measurements, wide-field FA, CFP, SD-OCT, SD-OCTA [where equipment is available], collection of ocular and non-ocular AEs, clinical laboratory evaluations, vital signs, ECGs, use of concomitant medications) 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 NPDR. 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

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 on Day 1 (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, Study EYP-1901-204

Dose (µg)	Number of Inserts per Single Applicator	Needle Gauge	Insert Length (mm)
2060	2	22	8
3090	3	22	8

6.1.2 EYP-1901/Sham Applicator Packaging

EYP-1901 is packaged at EyePoint Pharmaceuticals. EYP-1901 loaded applicators (and 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.

6.2 Study Drug Administration

6.2.1 EYP-1901 Intravitreal Insert

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 EYP-1901 Injection Procedure

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

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.

The Investigator has the overall responsibility of ensuring that EYP-1901 is 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. While the Investigator may delegate components of drug accountability tasks to

documented designee(s) (eg, 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 (ie, 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.

Since EYP-1901 is delivered through a pre-loaded applicator, the risk of accidental overdose is minimal. Refer to the current IB for information on potential risks associated with EYP-1901. Dose modification is not applicable since EYP-1901 is 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 airway 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 NPDR, both approved and investigational products. Previous treatments for NPDR are to be captured for the 12 months prior to Screening, and any historical anti-VEGF injections.

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 48 or Early Termination) must be documented on the concomitant medication eCRF.

Information 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 would also be considered prohibited concomitant medications.

All prohibited concomitant medications used concurrently (from Day 1 to Week 48 or Early Termination) must be documented on the concomitant medication eCRF

6.6.4 Permitted Medication and Procedures

Following the intravitreal injections of either dose of the EYP-1901 insert (2060 µg or 3090 µg) on Day 1, treatment of the fellow eye will be at the discretion of the Investigator. Any fellow eye therapy should be documented in concomitant meds during the study if required.

After Day 1, all subjects, regardless of treatment assignment, may receive approved anti-VEGF supplemental therapy or other standard of care therapy if they have ocular diabetic complications

warranting intervention. All ocular diabetic complications in the study eye will be managed in accordance with each study center's standard of care and must be documented as an AE.

During the study, participants who develop ocular diabetic complications in the study eye requiring anti-VEGF treatment per standard of care may be administered therapy as required. If needed, the study centers will provide their own supply of FDA-approved anti-VEGF therapy and submit the associated costs for reimbursement. The number of anti-VEGF injections received, the name of the product being injected, and the timing of all injections must be recorded in the source documents and eCRF.

Participants who develop ocular diabetic complications requiring PRP or retinal laser standard of care must have the time of laser treatment recorded in the source documents and eCRF.

Participants who develop ocular diabetic complications requiring surgical intervention standard of care (eg, pneumatic retinopexy, cryopexy, scleral buckle) must have the type of intervention and the time of intervention recorded in the source documents and eCRF.

In this case, the Investigator is required to contact the Medical Monitor prior to administering treatment if feasible.

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 (eg, 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 (eg, 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 (eg, 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 (eg, 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 (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).
- Progressive disease (NPDR) 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 (eg, 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 (ie, 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 (eg, increased dose of medication), based on medical evaluation (eg, 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, sham, 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 (ie, EYP-1901 or sham), 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 a 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, sham, 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:

PPD

The Investigator will also compile other relevant documentation with urgent priority (eg, 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" (ie, 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:

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:

PPD

7.2 Clinical Laboratory Evaluations

The clinical laboratory tests listed in the Study Laboratory Manual, including hematology, HbA1c, serum chemistry, coagulation, and urinalysis, will be done 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, treatment for the progression of NPDR may be required in the study eye for some subjects as a result of AEs or lack of efficacy of the study treatment. Intervention per the clinical sites standard of care are permitted (Section 6.6.4). Prohibited medications (Section 6.6.3), although discouraged, can be used if necessary (eg, 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 (eg, any failure of the applicator to deliver the intravitreal insert), or dissatisfaction with any other characteristic(s) of the drug product (eg, 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

Once all information is collected please report to:

PPD

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

PPD

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 exposure to vorolanib and X-297, its main metabolite, as measured through plasma. Blood 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 objective of this study is to assess the efficacy of EYP-1901 compared to sham treatment in the improvement of moderately severe to severe NPDR. The primary endpoint of this study will be the percentage of subjects improving ≥2 steps from baseline in the DRSS score at Week 36 in each EYP-1901 dose level versus the sham IVT injection group in the study eye.

The DRSS may be used to describe overall retinopathy severity as well as the change in severity over time. Severity ranges from level 10 (DR absent) to level 85 (advanced proliferative DR: posterior fundus obscured, or center of macula detached). Here, DRSS describes severity level 47 (moderately severe NPDR) and level 53 (severe NPDR) at Week 36 from baseline.

Additional secondary endpoints include the following in the study eye (unless otherwise specified):

- Percentage of subjects improving ≥2 steps from baseline in the DRSS score at Weeks 24 and 48 in each dose level vs. sham.
- Percentage of subjects improving ≥2-steps or ≥3-steps over time in DRSS from baseline.
- Percentage of subjects worsening ≥2-steps or ≥3-steps over time in DRSS from baseline.

- Percentage of subjects who developed a vision-threatening complication due to diabetic retinopathy at Weeks 24, 36, and 48.
- Percentage of subjects who developed CI-DME at Weeks 24, 36, and 48.
- Time to develop of any neovascular vision threatening complication (PDR/ASNV) through Weeks 24, 36 and 48.
- Time to develop CI-DME through Weeks 24, 36, and 48.
- Percentage of subjects who received anti-VEGF or additional standard of care intervention due to ocular diabetic complications at Weeks 24, 36, and 48.
- Percentage of subjects who received PRP, inclusive of subjects undergoing vitrectomy with endolaser, at Weeks 24, 36. and 48.
- Area under the curve (AUC) for change from baseline in BCVA at Weeks 24, 36, and 48.
- Systemic exposures to vorolanib and X-297, its main metabolite, measured through plasma levels up to Weeks 24 and 48.
- Rates of ocular (study eye and fellow eye) and non-ocular TEAEs at Weeks 24 and 48.

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 objectives of the study are to provide efficacy and safety data in a prospective, randomized, double-masked, controlled trial. However, the study is not formally powered to perform statistical hypothesis testing between each EYP-1901 arm versus sham IVT injection. Approximately 60 subjects will be randomized at 1:1:1 ratio to each of three treatment arms (20 per treatment arm).

11.2 Analysis Population

The intent-to-treat (ITT) population will include all subjects who received at least one dose of study treatment (EYP-1901 or sham). 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 treatment (EYP-1901 or sham) and continue until at least Week 36 (ie, 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 30 investigative study sites in the US will participate in the study. 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 36.

11.3.7 Multiple Comparisons and Multiplicity

Not applicable. This study is not powered for statistical significance hypothesis testing. All analysis will be descriptive.

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 9.4 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 percentage of subjects improving ≥2 steps from baseline in the DRSS score at Week 36 in each dose level vs. sham 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 PK data by treatment arm for the ITT population.

11.4.6 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.

11.4.7 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.

11.4.8 Clinical Laboratory Evaluations

Clinical laboratory evaluations (hematology, HbA1c, 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.

11.4.9 Vital Signs

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

11.4.10 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. Listing of prior and concomitant meds will be provided.

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.

14 REFERENCES

Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med. 1994;331(22):1480-1487.

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EYLEA® (aflibercept) prescribing information. Regeneron Pharmaceuticals, Inc. Tarrytown, NY. June 2021.

Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group: Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140:509-516.

Jackson TL, Boyer D, Brown DM, Chaudhry N, Elman M, et al. Oral tyrosine kinase inhibitor for neovascular age-related macular degeneration: a phase 1 dose-escalation study. JAMA Ophthalmol. 2017;135(7):761-767.

LUCENTIS® (ranibizumab injection) prescribing information. Genentech, Inc. South San Francisco, CA. March 2018.

Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmol. 1985;92:467-471.

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:

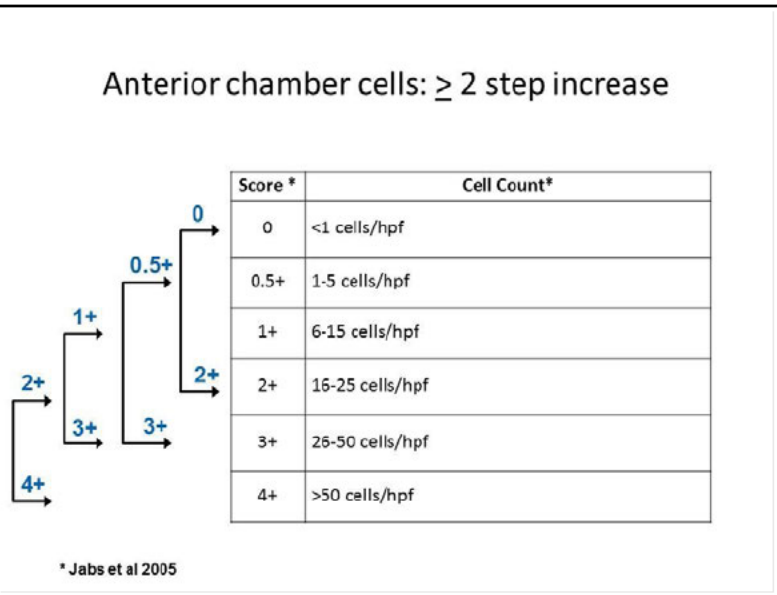
Anterior chamber cells will be measured using a Haag/Streit or similar slit lamp at high magnification (1.6 X) 1-mm beam. The same instrument, and when possible, the same examiner should be used on each patient throughout the study. Assessment will be made using the following scale (Jabs et al. 2005).

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.

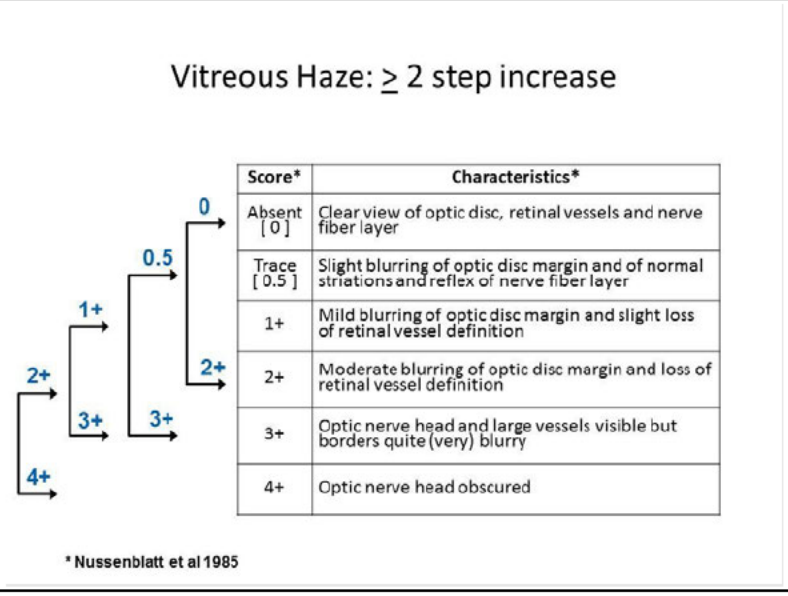
Vitreous Haze Grading Scale

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.



Score*	Characteristics*
Absent [0]	Clear view of optic disc, retinal vessels and nerve fiber layer
Trace [0.5]	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

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

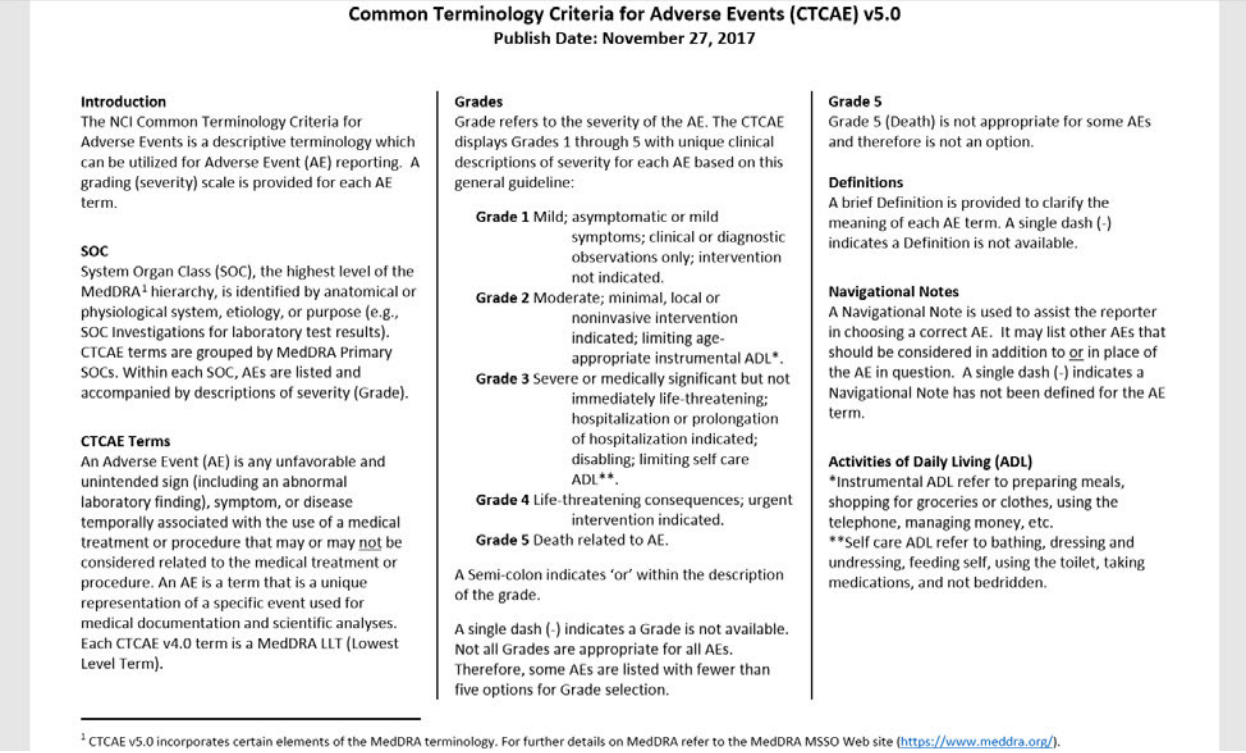
Intraocular pressure will be assessed by applanation tonometry (preferably, Goldmann) and should be measured before the slit lamp examination has been completed at all study visits and at the Day 1 visit , it should be measured at 10 (+/- 5) and 60 (+/- 10) minutes following the intravitreal injection (EYP-1901 or sham IVT 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 Laboratory 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-1901-204 as Amendment 1:

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 96 to Week 48, which allows for a 48-week follow-up from EYP-1901 administration. • Removed aqueous humor testing
Synopsis Section 2 Section 10	• The secondary endpoints were updated to reflect the new end of study at Week 48 instead of Week 96.
Synopsis Section 3.2 Section 5 Section 10 Section 11.3.6 Section 11.4.4	• Changed the unmasking of study data from Week 24 to Week 36. • Clarified only sponsor/CRO will be unmasked at Week 36
Section 3.2.1	• Renamed subsection as “Emergency Unmasking” for clarity.
Section 4.3	• Added “complete abstinence” as a highly effective method of birth control.
Table 5–1 Schedule of Assessments	• The Schedule of Assessments table was completely revised to reflect the change from Week 96 to Week 48 end of study visit. • The footnotes for Table 5-1 were also revised accordingly. • Removed aqueous humor testing
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. • Miscellaneous typographical, abbreviations, and formatting issues were corrected, and some hyperlinks were fixed and/or added.

The following changes were made to Protocol EYP-1901-204 as Amendment 2 (Version 3.0)

SECTION(S)	CHANGE/RATIONALE
Personnel contact information	• Changed the drug safety physician name to current Director of Pharmacovigilance.
Synopsis Section 3.1 Section 4 Section 11.1	• Adjusted the sample size to 60 subjects (20 subjects per treatment arm)
Section 1.5 Section 14	• Updated reference to Cohen et al. 2021.
Section 4	• Clarified the details regarding subject eligibility to assist Investigators when making decisions to reassess and rescreen subjects during the Screening Period
Section 3.4 Table 5–1 Section 5.1.1	• Increased the time of the Screening Visit to Day -30 to Day -5.
Section 5.1 Table 5–1 Section 5.1.3 to 5.1.7	• Increased the study visit window starting at Week 4 to Week 48 from 5 to 7 days.
Synopsis Section 10	• Clarified that the primary and secondary endpoint assessments were specifically for the study eye (unless otherwise specified).
Section 4.2	• As summarized in Administrative Letter#1 (25May2022), corrected the inconsistency in the Exclusion Criteria numbering between the Synopsis section of the protocol and the body of the protocol in Section 4.2. The method of numbering the Exclusion Criteria for both sections of the protocol were numbered sequentially.
Table 5–1 Section 5.1.1 to Section 5.1.7	• As summarized in Administrative Letter #2 (23June2022), updated the Schedule Procedures and Assessments to indicate that the intraocular pressure (IOP) measurements will be performed at all study visits.
Section 7.1.1	• As summarized in Administrative Letter #3 (10August2022), ocular adverse events was updated to define moderate or severe as Grade 2 and 3. Clarified the grading of ocular adverse events to provide consistency within the body protocol.
Table 5–1, footnote “e” Appendix 2	• As summarized in Administrative Letter #4 (04October2022), clarified the timing window for post-injection IOP at 10- and 60-minutes.
Section 6.6.4	• As summarized in Administrative Letter #4 (04October2022), clarified that after Day 1, a subject may be administered standard of care treatment at the Principal Investigators discretion.
Section 6.6.4	• Removed the statement “treatment for the fellow eye is not covered by the Sponsor”.
Synopsis Section 4.2	• As summarized in Administrative Letter #4 (04October202), Exclusion Criteria #8 was split into two separate exclusion criteria. An additional Exclusion Criteria #9 was created to state “any documentation of more than 4 prior anti-VEGF intravitreal injections in the study eye”.

SECTION(S)	CHANGE/RATIONALE
Section 7	• As summarized in Administrative Letter #5 (10January2023), removed the reference to safety review by a Drug Safety Committee (DSC). All safety reviews will be conducted by the Sponsor.
Synopsis Section 4.2	• Combined previous Exclusion Criteria #16 with #15 to provide clarity for those subjects who have undergone prior refractive or cataract surgery to create a new Exclusion Criteria #16.
Synopsis Section 4.2	• For Exclusion Criteria #33, added that subjects were excluded if any history of the stroke events within the past 2 years.
Throughout	• Miscellaneous typographical, abbreviations, and formatting issues were corrected, and some hyperlinks were fixed and/or added.