Statistical Analysis Plan for Interventional Studies

Text and Table, Figure, and Listing Shells

Sponsor Name:
EyePoint Pharmaceuticals, Inc.

Protocol Number:
EYP-1901-204

Protocol Title:
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 Version and Date:
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I confirm that I have reviewed this document and agree with the content.

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1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse event(s)
ANCOVA	Analysis of covariance
Anti-VEGF	Anti-vascular endothelial growth factor
ASNV	Anterior segment neovascularization
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BCVA	Best corrected visual acuity
CI	Confidence interval
CI-DME	Center involved-diabetic macular edema
CRC	Central reading center
CRF	Case report form
CST	Central subfield thickness
CTMS	Medidata Clinical Trial Management System
eCRF	Electronic case report form
DME	Diabetic macular edema
DRSS	Diabetic Retinopathy Severity Scale
ETDRS	Early Treatment Diabetic Retinopathy Study
EYP-1901	Vorolanib intravitreal [IVT] insert
FA	Fluorescein angiography
FAS	Full Analysis Set
HbA1c	Hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IOP	Intraocular pressure
IVT	Intravitreal
IXRS	Interactive voice/web response system
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum

Abbreviation	Description
n	Number of subjects
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
OD	Oculus dexter (right eye)
OS	Oculus sinister (left eye)
OU	Oculus uterque (both eyes)
PCS	Potentially clinically significant
PCSC	Potentially clinically significant change
PK	Pharmacokinetic(s)
PP	Per Protocol Set
PRP	Pan-retinal photocoagulation
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SD-OCT	Spectral-domain – optical coherence tomography
SD-OCTA	Spectral-domain – optical coherence tomography angiography
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TFL	Tables, figures, and listings
VEGF	Vascular endothelial growth factor
wAMD	Wet age-related macular degeneration
WHO	World Health Organization
X-297	Main metabolite of vorolanib

2. Introduction

This document describes the planned analyses that will be used for the Study EYP-1901-204 clinical study report. This randomized, double-masked, parallel study is designed to assess the safety, efficacy, and pharmacokinetics (PK) of vorolanib intravitreal insert (EYP-1901) compared to sham for the improvement in subjects diagnosed with moderately severe to severe non-proliferative diabetic retinopathy (NPDR). The purpose of this statistical analysis plan (SAP) is to ensure that the tables, figures, and listings (TFLs) which will be produced, and that the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives. This SAP is based on EYP-1901-204 Protocol Version 3 dated 31-Mar-2023.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all TFLs.

2.2. Timing of Final Analyses

The final analysis of safety, efficacy, and/or PK is planned after all subjects complete the final study visit (Week 48) or terminate early from the study, and all data is entered, cleaned, and locked. An unmasked, final, primary endpoint readout will take place after associated Week 36 data are entered and cleaned; only key individuals from sponsor and a specifically designated contract research organization team will be unmasked after the last subject completes the Week 36 visit.

3. Study Objectives

3.1. Primary Objective

The primary objective is to assess the efficacy of EYP-1901 (vorolanib intravitreal [IVT] insert) compared to sham treatment in the improvement of moderately severe to severe NPDR.

3.2. Secondary Objectives

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.

4. Study Details/Design

4.1. Brief Description

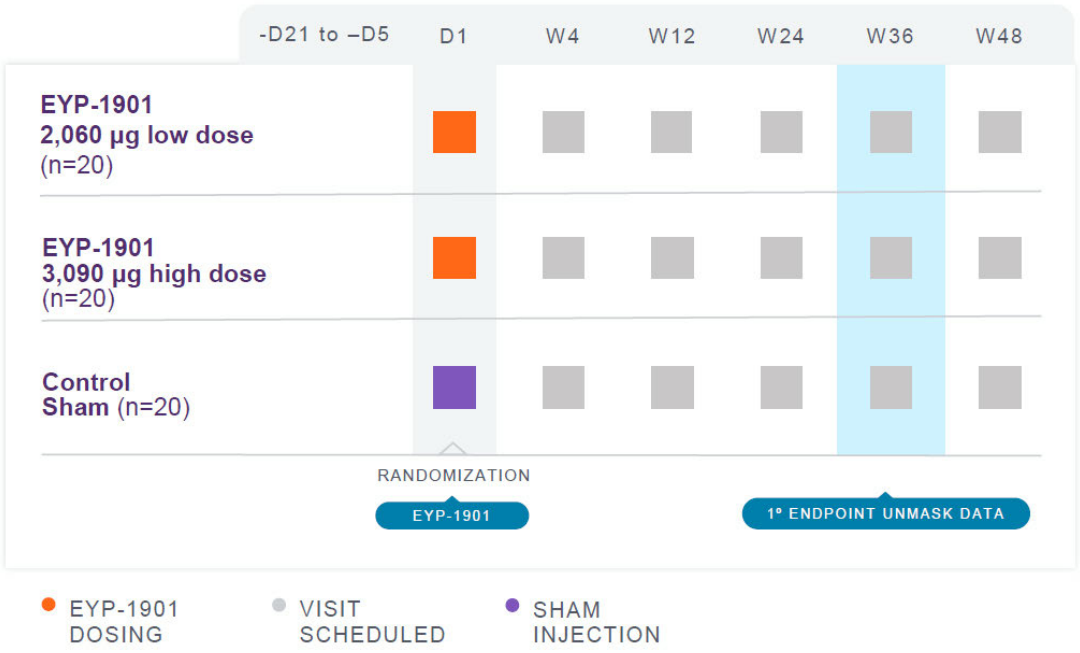
This is a prospective, randomized, double-masked, multicenter study evaluating the ocular efficacy and safety of 2 different doses of the EYP-1901 IVT insert compared to sham in adult subjects with NPDR. Approximately 60 subjects will be randomized in a 1:1:1 ratio to each of three treatment arms (2060 µg EYP-1901, 3090 µg EYP-1901, or sham IVT injection) across approximately 30 sites in the United States, such that each treatment arm will include approximately 20 subjects.

All subjects, irrespective of treatment arm, will receive an IVT injection on Day 1 in the designated study eye. Subjects in the EYP-1901 treatment arms will receive study treatment which is expected to deliver vorolanib into the vitreous humor for at least 9 months, while subjects in the sham treatment arm will receive a sham injection to maintain masking. Following study drug IVT injection on Day 1, subjects will return at Weeks 4, 12, 24, 36 and 48.

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.

The study design including treatment and visit schedules is shown in Figure 1.

Figure 1: Study Design



4.2. Subject Selection

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.

4.2.1. 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 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 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.

4.2.2. Exclusion Criteria

Subjects will be considered ineligible for participation in the study if any or all of the following exclusion criteria are satisfied:

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 2 or more classes of antiglaucoma medication) and any such condition which the Investigator feels may require a glaucoma filtering surgery while in the study.
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 3 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. 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 in a 1:1:1 ratio to each of 3 treatment arms (approximately 20 per treatment arm).

4.4. Treatment Assignment and Masking

This is a randomized, double-masked, parallel study. Subjects will be randomized to the 3 different treatment arms (2060 µg EYP-1901, 3090 µg EYP-1901, or sham IVT injection) in a 1:1:1 ratio. The randomization code will be generated with a computer program according to the study design, the number of subjects, and the number of treatment arms. 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.

Subjects, site staff, and the study team will be masked to treatment allocation during the study. The randomization code will be kept strictly confidential, accessible only to authorized personnel until the time of unmasking.

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 key individuals from sponsor/contract research organization team otherwise uninvolved in the study will be unmasked after the last subject completes the Week 36 visit to conduct endpoint analysis.

In the event that an emergency unmasking is required, the assessing Investigator/medically qualified designee has the authority to unmask a subject's treatment arm using the interactive voice/web response system (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.

The masking of the study will be broken after the database has been locked.

4.5. Administration of Study Medication

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. Each EYP-1901 IVT insert has been designed to deliver vorolanib into the vitreous humor for at least 9 months. Sham injections will be used to maintain masking of investigational EYP-1901 therapy for study subjects.

4.6. Study Procedures and Flowchart

An overview of the scheduled visits and measurements to be conducted during the study and their timing is presented in Table 1. Further details of the assessments are available in the protocol.

Table 1: Schedule of Study Procedures and Assessments for 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.

Footnotes for Table 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.

5. Endpoints

5.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the percentage of subjects improving ≥2 steps from baseline in the DRSS score in the study eye at Week 36 in each EYP-1901 dose level versus the sham IVT injection group.

5.2. Secondary Efficacy Endpoints

The secondary objectives will be assessed with the following secondary endpoints in each EYP-1901 dose level versus the sham IVT injection group:

- Percentage of subjects improving ≥2 steps from baseline in the DRSS score in the study eye at Weeks 24 and 48 in each EYP-1901 dose level versus the sham IVT injection group.
- Percentage of subjects improving ≥2 steps or ≥3 steps over time in DRSS score in the study eye from baseline.
- Percentage of subjects worsening ≥2 steps or ≥3 steps over time in DRSS score in the study eye from baseline.
- Percentage of subjects who developed a vision-threatening complication due to diabetic retinopathy in the study eye at Weeks 24, 36, and 48.
- Percentage of subjects who developed CI-DME in the study eye at Weeks 24, 36, and 48.
- Time to develop any neovascular vision threatening complication (PDR/ASNV) in the study eye through Weeks 24, 36, and 48.
- Time to develop CI-DME in the study eye through Weeks 24, 36, and 48.
- Percentage of subjects who received anti-VEGF or additional standard of care intervention due to ocular diabetic complications in the study eye at Weeks 24, 36, and 48.
- Percentage of subjects who received PRP in the study eye, inclusive of subjects undergoing vitrectomy with endolaser, at Weeks 24, 36, and 48.
- Area under the curve (AUC) for change from baseline in BCVA in the study eye at Weeks 24, 36, and 48.

5.3. Pharmacokinetic Endpoints

The PK endpoints are systemic exposure to vorolanib and X-297, its main metabolite, measured through plasma levels up to Weeks 24, 36, and 48.

5.4. Safety Endpoints

The safety endpoints are the rates of ocular (study eye and non-study eye) and non-ocular TEAEs at Weeks 24, 36, and 48.

6. Analysis Sets

6.1. Screened Set

The Screened Set will include all subjects screened (who have signed informed consent).

6.2. Full Analysis Set

The Full Analysis Set (FAS) will include all subjects who received study treatment (EYP-1901 or sham). Subjects will be assigned according to the treatment to which they were randomized. FAS will be used to summarize efficacy, demographic, and baseline data.

6.3. Per Protocol Set

The Per-protocol (PP) Set will include all subjects who received study treatment (EYP-1901 or sham), continue until at least Week 36 (i.e., have had the primary endpoint assessed), and have no major protocol deviation(s) that would significantly impact the primary endpoint. Subjects will be assigned according to the treatment actually received. PP will be used to summarize the primary efficacy endpoint as sensitivity analysis.

6.4. Safety Set

The Safety Set will include all subjects who received study treatment (EYP-1901 or sham). Subjects will be assigned according to treatment actually received. The Safety Set will be used to summarize treatment exposure and safety data.

6.5. Pharmacokinetic Set

The PK Set will include all subjects in the Safety Set for whom at least 1 evaluable PK sample is available.

7. Estimands

No estimands were defined within the protocol of this study.

8. General Aspects for Statistical Analysis

8.1. General Methods

- All analysis and summary outputs will be generated using SAS® version 9.4 or higher.
- Ocular data for both eyes are collected for each subject, but only 1 eye is identified as the study eye. Details regarding the presentation of individual analyses, that is, for study eye, non-study eye, or non-ocular, will be described in the relevant sections of this SAP as applicable.
- Continuous variables will be summarized using the number of subjects (n), mean, median, standard deviation (SD), minimum (min), and maximum (max).
- Categorical variables will be summarized using n and percentages of subjects.
- Time to event variables will be summarized using number and percentage of subjects with the event and censored and estimates of percentiles.
- All screened subjects will be included in subject data listings. Listings will be sorted by treatment arm, site, subject number, and date and time of assessment.
- Unscheduled visit data will be listed but not included in the by-visit summary tables, unless otherwise selected for analysis after application of visit windows (see Section 8.4).

8.2. Key Definitions

Baseline measurements are defined as the last non-missing measure prior to the initiation of study treatment, likely assessed at Screening or Day 1, but available unscheduled assessments will also be considered.

Study Day 1 will be the date on which study treatment is administered. Positive study days will be counted forward from Study Day 1, and negative study days will be counted backward from Study Day 1, beginning with Study Day -1. There will be no Study Day 0.

8.3. Missing Data

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

8.3.1. Medication Dates

A partial/missing start date recorded on the Prior and Concomitant Medications case report form (CRF) will be handled as follows:

- If only the day is missing, and the month and year match the month and year of study drug administration date, then the day of the study drug administration date will be imputed. Otherwise, the first of the month will be used.
- If both the day and month are missing, and the year matches the year of the study drug administration date, then the month and the day of the study drug administration date will be imputed. Otherwise, 01 January will be used.
- If the start date is completely missing, the study drug administration date will be imputed, unless the stop date is prior to the study drug administration date, then the stop date of the medication will be imputed and the medication will be considered to be a prior medication.

A partial/missing end date recorded on the Prior and Concomitant Medications CRF will be handled as follows:

- If only the day is missing, then the last day of the month will be imputed.
- If both the day and month are missing, then 31 December will be imputed.
- If the stop date is completely missing, or if the medication is ongoing, then the study completion or discontinuation date will be used.

8.3.2. Adverse Event Dates

In the event of a missing/incomplete start or stop date associated with an adverse event, only the treatment-emergence will be imputed using the algorithm below. Dates will not be imputed.

In general, if the missing/incomplete start date is not clearly prior to initiation of treatment, then the AE will be considered at TEAE.

If the AE end date is prior to the initiation of treatment, the AE will not be considered a TEAE.

If the AE end date is on or after the initiation of treatment:

- If the AE start date is completely missing or if the year is missing, then the AE will be considered a TEAE
- For partial AE start dates:
    - Known year, unknown month and day (or known year and day, unknown month)
        - If the year is the same as or later than the year of study drug administration, the AE will be considered a TEAE
        - Otherwise, the AE will not be considered a TEAE
    - Known year and month, unknown day
        - If the month and year are the same as or later than the month and year of the study drug administration, the AE will be considered a TEAE
        - Otherwise, the AE will not be considered a TEAE

8.4. Visit Windows

Safety and efficacy data will be analyzed per study visit. The named visit as recorded in the electronic Case Report Form (eCRF) will be displayed. Pre-specified visit windows are given in Table 2.

Table 2: Visit Windows for Endpoints Collected at All Visits

Visit	Target Study Day	Time Window	Visit Windows for Analysis
Screening	-21 to -5	NA	
Day 1	1	N/A	
Week 4	28	± 5 days	Study Days 2 to 56
Week 12	84	± 5 days	Study Days 57 to 126
Week 24	168	± 5 days	Study Days 127 to 210
Week 36	252	± 5 days	Study Days 211 to 294
Week 48	336	± 5 days	Study Days 295 to 350

Visit windows to be used for endpoints not collected at every visit are presented in Table 3, Table 4, and Table 5.

Table 3: Visit Windows for Wide-field Fluorescein Angiography

Visit	Target Study Day	Time Window	Visit Windows for Analysis
Screening	-21 to -5	NA	
Week 24	168	± 5 days	Study Days 2 to 210
Week 36	252	± 5 days	Study Days 211 to 294
Week 48	336	± 5 days	Study Days 295 to 350

Table 4: Visit Windows for Spectral-Domain – Optical Coherence Tomography Angiography (SD-OCTA)

Visit	Target Study Day	Time Window	Visit Windows for Analysis
Screening	-21 to -5	NA	
Week 24	168	± 5 days	Study Days 2 to 252
Week 48	336	± 5 days	Study Days 253 to 350

Table 5: Visit Windows for Clinical Laboratory Evaluations and PK

Visit	Target Study Day	Time Window	Visit Windows for Analysis
Screening (labs only)	-21 to -5	NA	
Day 1 (PK only)	1	NA	
Week 12	84	± 5 days	Study Days 2 to 126
Week 24	168	± 5 days	Study Days 127 to 210
Week 36	252	± 5 days	Study Days 211 to 294
Week 48	336	± 5 days	Study Days 295 to 350

Unscheduled and early termination visits will be associated with a visit according to the visit windows for analysis. Once visits are assigned for analysis, records will be flagged for analysis according to the following rules (in order):

- If a record is available for the scheduled visit, it will be used for analysis.
- If no record is available for the scheduled visit, the available windowed record will be used for analysis.
    - If more than 1 windowed record is available, the record closest to the target study day will be used for analysis.
    - If 2 windowed records are equidistant from the target study day, the windowed record after the target study day will be used.

Electrocardiogram (12-lead) and urine pregnancy data will be summarized at baseline and Week 48 / end of treatment using only nominal visit designators (no visit windows defined).

8.5. Pooling of Centers

No by-center analyses are planned.

8.6. Subgroups

Planned subgroup analyses are detailed in Section 10.1.

8.7. Multiple Comparisons and Multiplicity

Not applicable.

8.8. Adjustment for Covariates

Secondary efficacy endpoints will include baseline value as a covariate, when applicable.

9. Demographic, Other Baseline Characteristics and Medication

9.1. Subject Disposition and Withdrawals

Subject disposition and withdrawals from the study will be summarized for all subjects in the Screened Set and by treatment arm (for treated subjects) and overall to include the following:

- Number of subjects screened
- Number of screen failure subjects and primary reason for screen failure
- Number of subjects randomized
- Number (%) of randomized subjects in the FAS, PP Set, Safety Set, and PK Set
- Number (%) of subjects completing Week 36
- Number (%) of subjects who discontinued the study at or prior to Week 36 and primary reason for study discontinuation
- Number (%) of subjects completing the study
- Number (%) of subjects who discontinued the study early and primary reason for study discontinuation

A subject is considered to have completed the study if on the eCRF they have a date of completion and have no reason for study discontinuation reported.

9.2. Protocol Deviations

Protocol deviations may be identified during visits (via source data verification, for example) or after the fact, such as the site's reply to a data query that confirms that the protocol was not followed. For this project, collection of protocol deviations will be managed in the Medidata Clinical Trial Management System (CTMS) by the Site Monitor or Central Monitor during site visits or contacts. Protocol deviations will be reviewed by the Syneos Health team and the Sponsor, classified as major or minor deviations, and a list generated of subjects with significant deviations who are to be excluded from the Per-protocol Analysis Set; this list will be finalized and approved prior to database lock.

All protocol deviations, including COVID-19 related, will be listed by subject for the Safety Set.

Major protocol deviations will be summarized by treatment arm and overall for the FAS using counts and percentages of subjects.

9.3. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the FAS by treatment arm and overall. The following demographic variables will be listed and summarized:

- Age in years at screening
    - <40 years; 40 to <65 years; ≥65 years

  Age in years at screening will be computed using SAS code similar to the following:

  floor(YRDIF(<date of birth variable>, screen date, "AGE"))
- Sex (Male, Female)

- Child-bearing potential (Yes, No). If child bearing potential is "No", then reason will be summarized (surgically sterile, post-menopausal, other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (Asian, Black, White, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Unknown)
- Study Eye (OD, OS)

The following baseline characteristics will be listed and summarized:

- Baseline DRSS score in the study eye (43, moderate NPDR; 47, moderately severe NPDR; 53, severe NPDR)
- Baseline DRSS score in the study eye, categorical (≤47, ≥53)
- Baseline HbA1c
  - ≤8%; >8%
- Diabetes diagnosis to randomization (years)
- Baseline BCVA ETDRS letter score in the study eye
  - ≤55 letters; 56 – 70 letters; ≥71 letters
- Baseline CST in the study eye
  - ≤300 µm; >300 µm
- Number of anti-VEGF injections in the study eye prior to screening
  - 0 injections; 1 to 4 injections
- Time since diagnosis of NPDR in years at Screening in the study eye
  - Medical history terms, mapped and/or reported verbatim terms, will be examined by masked team members to identify those indicating NPDR, and the identified list will be logged in the programming specifications. The start date of earliest occurrence from amongst the identified events will be the NPDR diagnosis date and the time since diagnosis at screening will be calculated as screening date minus NPDR diagnosis date, plus 1. If the NPDR diagnosis date is missing only the day, the day will be set to 1, and if the NPDR diagnosis date is missing month and day (but not year), the month and day will be set to January 1.

Summaries will be using both categorical and continuous descriptive statistics, as detailed in Section 8.1. Unless otherwise specified, percentages will be calculated based on the n in the respective population.

9.4. Medical History

Medical history (inclusive of medical, surgical, and ophthalmic history) will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or higher. Incidence of ocular medical history for the study eye, ocular medical history for the non-study eye, and non-ocular medical history will be separately summarized by system organ class (SOC) and preferred term (PT) for the Safety Set by treatment arm and overall. Incidence of medical conditions will be presented alphabetically by SOC and then within each SOC, alphabetically by PT for the overall column.

9.5. Prior and Concomitant Medications

Medications will be coded using the most recent version of the World Health Organization Drug Dictionary (Global B3 September 2021 Version). Missing medication dates will be handled as described in Section 8.3.1. Anti-VEGF medications will be identified via review of standardized medication terms and flagged in the data.

Start date and stop date for medications, in conjunction with the ongoing indicator, from the eCRF will be used to determine whether medication is prior or concomitant.

Prior medication will be defined as all medications recorded on the “Concomitant Medication” CRF taken prior to study drug administration, whether continuing or not.

Concomitant medications will be defined as medications that are ongoing at study treatment administration or started on or after study treatment administration.

The number and percentage of subjects by treatment arm and overall in the Safety Set for prior medication (ocular study-eye, ocular non-study eye, and non-ocular summarized separately) and concomitant medication (ocular study eye, ocular non-study eye, and non-ocular summarized separately) will be summarized by Anatomical Therapeutic Chemical (ATC) level 2 and PT. They will be presented by descending overall count of ATC and within each ATC, by descending overall count of PT. Subjects will be counted only once for each ATC and PT if they have multiple records of the same ATC or PT in the database.

Prior to database lock, the sponsor will conduct a masked data review of medications to determine if any are classified as prohibited medications per the protocol; prohibited medications (if any) will be flagged in the prior and concomitant medication listings.

9.6. Study Drug Exposure

The number and percentage of randomized subjects who had study drug administered and who did not have study drug administered (overall and broken out by adverse event and other reason) will be summarized by treatment group and overall. The number and percentage of subjects to whom study drug was administered who had and did not have clinically significant signs/symptoms observed following injection will also be summarized by treatment group and overall.

Study drug exposure data will be presented in a data listing, including information as to whether the study drug IVT was administered, the date and time of the administration, and any clinically significant signs/symptoms observed.

10. Efficacy

All efficacy endpoints will be summarized descriptively by treatment arm and for EYP-1901 overall for the FAS; summarization and analyses will be repeated for the PP Set as sensitivity analyses. For continuous endpoints, n, mean, SD, median, min, and max will be presented. For categorical endpoints, numbers and percentages will be presented. The 95% confidence interval (CI) of the proportions will be constructed, as appropriate.

PPD

10.1. Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is the percentage of subjects improving ≥2 steps from baseline in the DRSS score at Week 36 in the study eye. The percentage of subjects improving ≥2 steps from baseline in the DRSS score will be summarized descriptively using counts and percentages of subjects by randomized treatment arm at each scheduled visit (Weeks 4, 12, 24, 36, and 48) and the corresponding 95% Clopper-Pearson CI will be presented for each treatment group. PPD

Subgroup Analysis

The summarization and analyses (not plots) of the primary efficacy endpoint will be repeated for FAS for the following subgroups:

- Age at screening (<40 years; 40 to <65 years; ≥65 years)
- Sex (male, female)
- Baseline DRSS score in the study eye of 43 (moderate NPDR), 47 (moderately severe NPDR), and 53 (severe NPDR)
- Baseline DRSS score in the study eye, categorical (≤47, ≥53)
- Baseline BCVA ETDRS letter score in the study eye
    - ≤ median; > median
    - ≤55 letters; 56 to 70 letters; ≥71 letters
- Baseline CST in the study eye
    - ≤300 microns
    - >300 microns
- Number of anti-VEGF injections in the study eye prior to screening
    - 0 injections
    - 1-4 injections
- Baseline HbA1c (≤8%; >8%)

- Years from NPDR diagnosis to screening
    - ≤ median; > median
    - ≤2 years; >2 to 4 years; >4 years

PPD

10.2. Secondary Efficacy Endpoint Analyses

Response Endpoints

The analysis and summarization performed for the primary endpoint (Section 10.1) will be repeated for the following secondary efficacy endpoints.

- Percentage of subjects improving ≥2 steps from baseline in the DRSS score in the study eye at Weeks 24 and 48.
- Percentage of subjects improving ≥2 steps from baseline in the DRSS score in the study eye at each timepoint (remaining timepoints apart from Weeks 24, 36, and 48)
- Percentage of subjects worsening ≥2 steps from baseline in the DRSS score in the study eye at each timepoint
- Percentage of subjects improving ≥3 steps from baseline in the DRSS score in the study eye at each timepoint
- Percentage of subjects worsening ≥3 steps from baseline in the DRSS score in the study eye at each timepoint
- Percentage of subjects who developed a vision-threatening complication due to diabetic retinopathy in the study eye through Week 24, through Week 36, and through Week 48.

  Vision threatening complications due to diabetic retinopathy will be indicated by the presence of "Vitreous hemorrhage" or the presence of "Tractional retinal detachment" reported on the Ocular Examination – Dilated Ophthalmoscopy CRF (proliferative diabetic retinopathy [PDR] events, and "Neovascularization for the Iris" answered as "Yes" or "Neovascularization for the Angle" answered as "Yes" per the Ocular Examination - Slit Lamp Biomicroscopy CRF (anterior segment neovascularization [ASNV] events).

  Summarization and analyses will be repeated for the following subgroups – baseline DRSS in the study eye of 43 (moderate NPDR), 47 (moderately severe NPDR), and 53 (severe NPDR), and baseline DRSS score in the study eye, categorical (≤47, ≥53).

- Percentage of subjects who developed CI-DME in the study eye through Week 24, through Week 36, and through Week 48.

  The occurrence of a CI-DME event in the study eye will be identified via examination of centrally read custom algorithm CST data and adverse events. For the CST data at any given time point, if results are available for no more than 2 raters, the average value will be used, and if results are available for three raters, the median value will be used. CI-DME will have occurred when an adverse event occurs which has a mapped preferred term of ‘Cystoid macular oedema', 'Diabetic retinal oedema', or 'Macular oedema', for which the temporally closest CST measurement is greater than or equal to 320 microns.

  Two additional endpoints will also be summarized.

  - Macular edema (Definition 1) will have occurred when an adverse event occurs which has a mapped preferred term of ‘Cystoid macular oedema', 'Diabetic retinal oedema', or 'Macular oedema'.
  - Macular edema (Definition 2) will have occurred when an adverse event occurs which has a mapped preferred term of ‘Cystoid macular oedema', 'Diabetic retinal oedema', or 'Macular oedema', and which has treatment with a concomitant medication with a mapped preferred term of ‘aflibercept’, ‘ranibizumab’, ‘bevacizumab’, or ‘faricimab’.

- Percentage of subjects who received anti-VEGF or additional standard of care intervention due to ocular diabetic complications in the study eye through Week 24, through Week 36, and through Week 48.

  Anti-VEGF use is identified in reported concomitant medication data as those medications with ATC code ‘S01LA’.

  Unique mapped concomitant medication and procedure terms and associated information will be reviewed by masked ophthalmology team members to identify those mapped concomitant medication and procedure terms that indicate the use of additional standard of care intervention due to ocular diabetic complications.

- Percentage of subjects who received PRP in the study eye, inclusive of subjects undergoing vitrectomy with endo-laser, through Week 24, through Week 36, and through Week 48.

  Unique mapped procedure terms and associated information will be reviewed by masked ophthalmology team members to identify those mapped procedure terms that indicate receipt of PRP.

Time to Event Endpoints

Time (in weeks) to develop any vision threatening complication (PDR/ASNV) in the study eye through a particular time point (Week 24, Week 36, or Week 48) will be computed as the earliest date of a vision threatening complication in the study eye prior to the particular time point minus the date of study drug administration, plus 1 day, divided by 7 days per week. For subjects not experiencing a vision threatening complication in the study eye prior to the particular time point of interest, the subject will be censored at their date of discontinuation from the study (if prior to the time point of interest) or at the time point of interest.

Time (in weeks) to develop a CI-DME in the study eye, macular edema in the study eye per Definition 1, and macular edema in the study eye per Definition 2 will be computed in a similar manner.

Each time to event endpoint will be summarized with the number and percentage of subjects who experienced the endpoint, number and percentage of subjects who were censored, and Kaplan-Meier estimates of median and first and third quartiles. The EYP-1901 treatment arms will be compared to the sham IVT group using a log-rank test. A corresponding Kaplan-Meier plot will be prepared for the FAS only.

Area Under the Curve Endpoint

Observed BCVA values, change from baseline to each follow-up visit, and area under the curve (AUC) for change from baseline in BCVA through Week 24, Week 36, and Week 48 will be summarized descriptively. AUC through each time point of interest will be computed using the trapezoidal rule normalized to months, with a final unit of letters. Mean AUC for change from baseline in BCVA through Week 24, Week 36, and Week 48 will be compared between each active treatment arm and sham IVT using analysis of covariance (ANCOVA) with treatment arm as the main effect and baseline BCVA as a covariate. A plot of mean change from baseline in BCVA score over time will be prepared for the FAS.

Change from Baseline in DRSS Step

DRSS scores (not including indeterminate results) will be coded to numeric values for change in step analysis as indicated in Table 6.

Table 6: Mapping of DRSS Scores to Numeric Steps

DRSS Score	Coded Numeric Step
10	0
20	1
35	2
43	3
47	4
53	5
61	6
65	7
71	8
75	9
85	10

The coded numeric values represent whole steps on the DRSS, where Step 0 is no diabetic retinopathy and Step 10 is advanced proliferative diabetic retinopathy. Baseline is defined as the last non-missing DRSS measurement prior to the initiation of study treatment. Change from baseline is computed as follow-up step minus baseline step; a negative change indicates improvement in disease and a positive change indicates worsening of disease.

Observed values and change from baseline will be summarized descriptively by treatment group for the full analysis set.

The SAS MIXED procedure (MMRM) will be used with the REPEATED statement for visits with an unstructured covariance structure and a RANDOM statement set at the subject level. The model will include change from baseline at each visit as the dependent variable and fixed effects for treatment and visit and the interaction between treatment and visit, and baseline DRSS step as a covariate. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. If there is a convergence issue (lack of convergence in general, or convergence with a non-positive definite estimated

G-matrix or non-positive definite Hessian matrix) with the unstructured covariance structure, a Toeplitz or Autoregressive (1) [AR(1)] covariance structure will be used, following this sequence, until convergence is achieved. If the model still does not converge, no results will be reported. Model-based point estimates (i.e., least squares means and least squares mean differences, 80%, 85%, 90%, 95%, and 97.5% CI, and p-values) will be reported at each visit.

11. Safety

Safety assessments will include the incidence and severity of TEAEs, clinical laboratory evaluations (hematology, chemistry, coagulation, and urinalysis), vital sign measurements, ECGs, IOP measurements, and safety data collected from ocular examinations. Safety analyses will be based on the Safety Set.

11.1. Adverse Events

All AEs will be coded using the most recent version of MedDRA, version 25.0 or higher, and will be presented in the following data listings by SOC and PT for each subject.

- All AEs
- Ocular AEs
- AEs related to study treatment
- Serious adverse events (SAEs)
- SAEs related to study treatment
- AEs with an outcome of death
- AEs leading to study treatment discontinuation
- AEs leading to study withdrawal

Treatment-emergent adverse events (TEAEs) are AEs that began on or after the date of study treatment administration. Missing/incomplete start or stop dates associated with an adverse event (AE) will be handled as per Section 8.3.2 to determine whether an AE is a TEAE. The following categories of TEAEs will be summarized by treatment arm and overall for the Safety Set using count and percentage of unique subjects experiencing a TEAE and number of events for each TEAE by SOC and PT. An overall summary table will also be produced to summarize the following categories of TEAEs.

- All TEAEs
- TEAEs related to study treatment
- Serious TEAEs
- Serious TEAEs related to study treatment
- TEAEs by maximum severity (mild [Grade 1], moderate [Grade 2], severe [Grade 3], life/sight-threatening [Grade 4], death [Grade 5]), total number of events at each severity summarized
- TEAEs by worst relationship (not related, possibly related, probably related), total number of events at each relationship summarized
- TEAEs leading to study treatment discontinuation
- TEAEs leading to study withdrawal

Summaries will be presented separately by location of the TEAEs (ocular in study eye, ocular in non-study eye, and non-ocular), and will be sorted by overall descending count of SOC and then, within a SOC, by overall descending count of PT. Subjects will only be counted once if they experience multiple events under the same SOC or PT, and at the maximum severity or worst relationship, as applicable.

Summaries by SOC and PT (not by maximum severity or worst relationship) will also include a summarization of the number and percentage of subjects with more than 1 TEAE.

Summaries of TEAEs (ocular in study eye, ocular in non-study eye, and non-ocular) by PT only will be presented by treatment arm and overall, sorted by overall descending count of PT. Subjects will only be counted once if they experience multiple events under the same PT.

11.2. Laboratory Evaluations

All statistical analyses of laboratory values will be performed using SI units.

Some numeric lab values may be reported as '<n.n' or '>n.n'; these will be analyzed in the summary statistics as n.n/2 and n.n, respectively. For example, triglycerides recorded as <0.50 mmol/L would be summarized as 0.25 mmol/L and potassium recorded as >6.0 mmol/L would be summarized as 6.0 mmol/L.

Continuous hematology including coagulation, HbA1c, chemistry, and urinalysis results (raw and change from baseline) will be summarized by actual treatment arm and overall at each scheduled visit for the Safety Set. Categorical urinalysis results will be summarized by frequencies and percentages at each scheduled visit for the Safety Set. The number and percentage of subjects with shift changes from baseline based on the laboratory normal ranges provided by the laboratory will be tabulated at each scheduled visit.

Hematology including coagulation, chemistry, and urinalysis data will be listed with the values outside the normal ranges flagged. Pregnancy test results will be listed but not summarized.

11.3. Vital Signs

Vital signs will include pulse rate, respiration rate, body temperature, and systolic and diastolic blood pressure; the average of 3 readings will be taken in a resting state and reported on the eCRF. Vital sign results (systolic and diastolic blood pressure [mmHg], pulse rate [beats/min], body temperature [°C], and respiration rate [breaths/min]) and changes from baseline will be summarized by scheduled visit and by treatment arm and overall for the Safety Set.

Potentially clinically significant (PCS) values will be identified for vital sign parameters as outlined in Table 6; these values will be summarized by scheduled visit and by treatment arm and overall for the Safety Set. Any vital sign results considered clinically significant by the investigator will be captured as adverse events.

Vital sign results will be listed by subject and timing of collection.

Table 6: Potentially Clinically Significant Values for Vital Sign Parameters

Vital Sign	Units	Criteria for PCS Values (Observed values)		Criteria for PCSC values (Change from Baseline values)	
		High	Low	Increase	Decrease
Systolic Blood Pressure	mmHg	>180	<90	≥30	≥30
Diastolic Blood pressure	mmHg	>110	<50	≥20	≥20

11.4. Electrocardiograms

For each ECG measurement (heart rate and PR, QRS, QT, and QTcF intervals), the observed value at each scheduled visit and change from baseline at each scheduled visit will be summarized by treatment arm and overall for the Safety Set.

In addition, the number and percentage of subjects with PCS and potentially clinically significant change (PCSC) values will be summarized by scheduled visit and for any time post-baseline, by treatment arm and overall for the Safety Set. PCS and PCSC values will be identified for ECG parameters as outlined in Table 7.

A shift table of overall ECG interpretation from baseline to scheduled post-baseline visits will be presented for the categories 'Normal' and 'Abnormal'. The shift table will be presented by visit and treatment arms.

Clinically significant abnormal findings will be reported as adverse events. The values of each ECG parameter will be listed by subject.

Table 7: Potentially Clinically Significant Values for QTcF

Units	Criteria for PCS Values (Observed Values)		Criteria for PCSC Values (Change from Baseline)	
	High	**Low**	**Increase**	**Decrease**
msec	≤ 450 msec > 450 msec and ≤480 msec > 480 msec and ≤500 msec > 500 msec	NA	≤ 30 msec > 30 msec and ≤ 60 msec > 60 msec	NA

11.5. Intraocular Pressure Measurement

For IOP, the observed value at each scheduled visit and change from baseline at each scheduled visit will be summarized descriptively by treatment arm and overall for the Safety Set, for study eye and non-study eye. This summarization will include the number and percentage of subjects at each visit with observed IOP ≤25 mmHg and >25 mmHg, and the number and percentage of subjects with change from baseline ≤10 mmHg and >10 mmHg.

The IOP data will also be listed by subject.

11.6. Ocular Examinations

The observed values of categorical dilated ophthalmoscopy and slit lamp biomicroscopy parameters at each scheduled visit will be summarized by treatment arm and overall for the Safety Set for study eye and non-study eye. The ocular examination parameters will also be listed by subject.

SD-OCT, SD-OCTA, and color fundus data will be presented in data listings.

11.7. Best Corrected Visual Acuity

Observed BCVA values and change from baseline to each follow-up visit are to be summarized descriptively (n, mean, SD, median, min, and max) for the FAS (identical to the Safety Set) by treatment arm and overall for the study eye and non-study eye as part of the efficacy analysis (Section 10.2).

The following endpoints will be summarized descriptively for the Safety Set by treatment arm and overall for the study eye using counts and percentages of participants at each scheduled visit and a corresponding 95% Clopper-Pearson CI for proportion with response by treatment group. The difference in the proportion of subjects with the desired response will be presented for each active treatment arm minus sham IVT, and the corresponding 95% Chan-Zhang CI presented.

- Proportion of subjects with ≥5 BCVA letter loss
- Proportion of subjects with ≥5 BCVA letter gain

- Proportion of subjects with ≥10 BCVA letter loss
- Proportion of subjects with ≥10 BCVA letter gain
- Proportion of subjects with ≥15 BCVA letter loss
- Proportion of subjects with ≥15 BCVA letter gain

12. Pharmacokinetics

12.1. Pharmacokinetic Endpoints

The PK endpoint is systemic exposure to vorolanib and X-297, its main metabolite, measured through plasma levels up to Weeks 24, 36, and 48.

12.2. Pharmacokinetic Sampling

The plasma samples will be collected at Day 1, Weeks 12, 24, 36, and 48, and any early termination visit.

12.3. Data Presentation

Descriptive statistics of plasma concentrations by treatment arm will be presented for the PK Set; when calculating drug concentration descriptive statistics, values below the limit of quantification (BLQ) will be considered zero. Plasma concentration data will also be listed. The following plots, for the study drug vorolanib and X-297, its main metabolite, will be prepared.

- Linear and log-linear scale of mean (±SD) plasma concentrations versus scheduled time points.
- Linear and log-linear scale spaghetti plots of individual subject plasma concentrations versus actual time points by dose level

13. Interim Analyses

No interim analyses are planned for this study prior to the primary endpoint readout at Week 36. A final analysis of the primary efficacy endpoint will take place at Week 36 prior to the end of the study, once all subjects have completed Week 36 or discontinued early and all necessary data have been cleaned and finalized. A data snapshot will be taken and Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets and necessary tables, figures, and listings will be generated and quality checked in a masked manner. Once the masked data and outputs are reviewed and approved by the masked sponsor team, the programming system will be transferred to an unmasked biostatistics team at Syneos Health, who will generate and quality check the package run in an unmasked manner and distribute it to a limited number of pre-specified individuals. The unmasked biostatistics team at Syneos Health serving in this capacity will be otherwise uninvolved in the conduct of the study through database lock and full unmasking of the study.

14. Changes from Analyses Planned in Protocol

Changes from the analyses planned in the protocol include the following.

- Whereas Protocol Section 11.3.5 indicates that there will be no adjustment of analyses for covariates, secondary efficacy endpoints will include baseline value as a covariate, when applicable (SAP Section 8.8).
- The protocol defines the ITT population as all subjects who received at least one dose of study treatment and defines the efficacy population as ITT subjects who continue to at least Week 36, having the primary efficacy endpoint assessed. This SAP instead defines the FAS and Safety Set, which are both the equivalent of the protocol-defined ITT, and the PP Set, which is the equivalent of the protocol-defined efficacy population with the added criterion of subjects having no protocol deviation(s) that would significantly impact the primary endpoint. This change from the protocol in analysis set definitions is consistent with the approach taken for the EYP-1901-201 study.

15. Reference List

There are no references applicable for this SAP.

16. Programming Considerations

All tables, figures, listings (TFLs), and statistical analyses will be generated using SAS for Windows, Release 9.4 (SAS Institute Inc., Cary, NC, United States of America). Computer-generated table, listing, and figure output will adhere to the following specifications.

16.1. General Considerations

- One SAS program can create several outputs.
- One output file can contain several outputs.
- Output files will be delivered in Rich Text File format, readable in Microsoft Word.
- Numbering of TFLs will follow International Conference for Harmonization (ICH) E3 guidance.

16.2. Table, Figure, and Listing Format

16.2.1. General

- All TFLs will be produced in landscape format on American letter size, unless otherwise specified
- All TFLs will be produced using the Courier New font, size 8, which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8, which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

16.2.2. Headers

- All output will have the following header at the top left of each page:
- EyePoint Pharmaceuticals, Inc., Protocol EYP-1901-204
- Draft/Final Run <*date*>
- All output will have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number will appear sequentially as page n of N, where N is the total number of pages in the table).

- The date the output was generated will appear along with the program name as a footer on each page.

16.2.3. Display Titles

- Each TFL is identified by the designation and a numeral, i.e., Table 14.1.1. A decimal system (x.y and x.y.z) is used to identify TFLs with related contents. The title is centered. The analysis set is identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z

First Line of Title

Second Line of Title if Needed

Full Analysis Set

16.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column is on the far left followed by the treatment arm columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment arm.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment arm in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatment arms in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

16.2.5. Body of the Data Display

16.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values will be left-justified;
- Whole numbers (e.g., counts) will be right-justified; and
- Numbers containing fractional portions will be decimal aligned.

16.2.5.2. *Table Conventions*

- Units will be included where available
- For categorical parameters, all categories will be presented in the table, even if n=0 for all treatment arms in a given category. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
Severe	0
Moderate	8
Mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- An Unknown or Missing category will be added to each parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values will be printed out to 1 more significant digit than the original values, and standard deviations will be printed out to 2 more significant digits than the original values. The minimum and maximum will report the same significant digits as the original values. For example, systolic blood pressure will be presented as follows:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values will be output in the format ‘0.xxx’, where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If a p-value should be less than 0.0001, then present as <0.0001. If a p-value is returned as >0.999, then present as >0.999.
- Percentage values will be printed to 1 decimal place, in parentheses with no spaces, 1 space after the count (e.g., 7 (12.8%), 13 (5.4%)). A pre-determination will be made regarding how to display values that round down to 0.0; a common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment arm who have an observation will be the denominator. Percentages after zero counts will not be displayed and percentages equating to 100% will be presented as 100%, without decimal places.
- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data will be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment arm in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) will be displayed in decreasing order. If incidence for more than 1 term is identical, they will then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated will be reported as ‘-’

- The percentage of subjects will normally be calculated as a proportion of the number of subjects assessed in the relevant treatment arm (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Details will be described in footnotes or programming notes, as necessary.
- For categorical summaries (number and percentage of subjects) where a subject can be included in more than 1 category, a footnote or programming note will be added describing whether the subject is included in the summary statistics for all relevant categories or just 1 category as well as the selection criteria.
- Where a category with a subheading (such as SOC) has to be split over more than 1 page, output the subheading followed by '(cont)' at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

16.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment arms as above, subject number, visit/collection day, and visit/collection time.
- Dates will be printed in SAS DATE9.format ('DD_MMM_YYYY': 01JUL2000).
- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26 or 11:26:45). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

16.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment arm mean change from Baseline) values will be displayed on the Y-axis.

16.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes will always begin with 'Note:' if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote will start on a new line, where possible.
- Subject specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the TFL. If more than 6 lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, the date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').
- Sources and/or cross-references in footnotes will use the keyword prefix (in singular form) for each reference and will be separated by a comma when multiple cross-references are displayed.
  Example
  Reference: Listing 16.2.4.1.1, 16.2.4.1.2, 16.2.4.2.1

17. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures, or statistical analyses. An overview of the development of programs is detailed in Syneos Health Developing Statistical Programs Standard Operation Procedure (3907).

Syneos Health Developing Statistical Programs Standard Operating Procedure (3907), Conducting the Transfer of Biostatistical Deliverables Standard Operating Procedure (3908), and the SAS Programming and Validation Plan describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency, and commenting, and by review of the produced output.

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