16.1.9 Documentation of Statistical Methods

The document listed below is provided in this section.

Statistical Analysis Plan (EYP-1901-201) Version 2.0 dated 15-February-2024

Statistical Analysis Plan for Interventional Studies

Text and Table, Figure, and Listing Shells

Sponsor Name:
EyePoint Pharmaceuticals, Inc.

Protocol Number:
EYP-1901-201 / **NCT05381948**

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

Protocol Version and Date:
6.0, 25-Jan-2024

Syneos Health Project Code:
7032905

Author:
PPD , Principal Biostatistician

Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
0.1	25-Aug-2022	PPD	Initial Release Version
0.2	31-Jan-2023	PPD	Updates per sponsor and internal review comments and protocol amendment.
0.3	20-Mar-2023	PPD	Updates per sponsor.
0.4	21-Apr-2023	PPD	Updates per sponsor.
0.5	25-May-2023	PPD	Updates per sponsor.
0.6	26-May-2023	PPD	Updates per sponsor.
0.7	31-Oct-2023	PPD	Updates per dry run work and sponsor comments/communications.
0.8	09-Nov-2023	PPD	Updates per sponsor.
0.9	13-Nov-2023	PPD	Addition of sensitivity analysis for primary endpoint.
1.0	16-Nov-2023	PPD	Updates per sponsor.
1.1	09-Feb-2024	PPD	Incorporated updates from Version 6 protocol; corrected some typographical errors; added clarifying edits to description of primary endpoint sensitivity analyses; added summarization of treatment burden in study eye normalized to 6 months and normalized to 12 months.
1.2	15-Feb-2024	PPD	Corrected upper limit of Week 32 visit window and lower limit of Week 36 visit window, and removed unnecessary "Safety Follow-up" window. Section 9.5: Changed "continuing" to "ongoing" for consistency. Section 10.1: Updated text to indicate what constitutes a convergence issue for the mixed model.
2.0	15-Feb-2024	PPD	Version updated from 1.2 to 2.0; modifications to signature page.

I confirm that I have reviewed this document and agree with the content.

Approvals

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1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse event(s)
AMD	Age-related macular degeneration
ATC	Anatomical Therapeutic Chemical
BCVA	Best corrected visual acuity
BLQ	below the limit of quantification
CI	Confidence interval
CNV	Choroidal neovascularization
CST	Central subfield thickness
eCRF	Electronic case report form
FA	Fluorescein angiography
FAS	Full Analysis Set
ETDRS	Early Treatment Diabetic Retinopathy Study
HIPAA	Health Insurance Portability and Accountability
ICH	International Conference on Harmonization
IOP	Intraocular pressure
LOCF	last observation carried forward
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing Not at Random
NYHA	New York Hospital Association
OD	oculus dexter (right eye)
OS	oculus sinister (left eye)
PK	Pharmacokinetic(s)
PP	Per-protocol
RPED	Retinal pigment epithelium detachment
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SD-OCT	Spectral-domain – optical coherence tomography

Abbreviation	Description
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
VEGF	Vascular endothelial growth factor
wAMD	Wet age-related macular degeneration

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables, and figures 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.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, figures, and listings.

2.2. Timings of Analyses

The final analysis of safety, efficacy, and pharmacokinetics (PK) is planned after all subjects complete the final study visit or terminate early from the study, and all data is entered, cleaned, and locked.

3. Study Objectives

3.1. Primary Objective

The primary objective is to evaluate the efficacy of two doses (2,060 µg and 3,090 µg) of the EYP-1901 intravitreal insert on visual acuity compared to aflibercept.

3.2. Secondary Objective(s)

The secondary objectives are to evaluate the use of rescue treatments (or “supplemental injections”) in the study eye, the retinal functional and anatomical response to treatment, and the safety following treatment with EYP-1901 intravitreal insert compared to aflibercept.

4. Study Details/Design

4.1. Brief Description

The design for this study is a prospective, randomized, double-masked, multicenter trial comparing two different doses of the EYP-1901 intravitreal insert to aflibercept in previously-treated subjects (≥50 years of age) with wet age-related macular degeneration (wAMD). Approximately150 subjects will be randomized on a 1:1:1 basis to the 3 different treatment arms (2,060 µg EYP-1901, 3,090 µg EYP-1901, or 2 mg [0.05 mL] aflibercept) across approximately 70 sites, such that each arm will include up to 50 subjects.

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

All subjects, irrespective of treatment arm, will receive a dose of aflibercept on Day 1 and Week 4 in the designated study eye. At Week 8, all subjects will receive a third aflibercept injection and subjects in the EYP-1901 treatment arms will receive the assigned dose of the EYP-1901 intravitreal insert 30 minutes (+/- 10 minutes) following aflibercept injection, which is expected to deliver vorolanib into the vitreous humor for at least 9 months, while subjects in the aflibercept treatment arm will receive a sham injection 30 minutes (+/- 10 minutes) following aflibercept injection to maintain masking.

Subjects in the aflibercept arm will be re-treated with aflibercept at Week 16 and every 8 weeks thereafter, or when pre-defined re-treatment criteria are met (see details in Protocol Section 6.6.4 Rescue Treatment), while subjects in the EYP-1901 treatment arms will receive a sham injection (or aflibercept when the pre-defined re-treatment criteria are met) during these visits. Follow-up examinations will be conducted at Week 12, and every 4 weeks thereafter up to Week 56.

4.2. Subject Selection

Subjects will be enrolled in the study if they meet all the inclusion and none of the exclusion criteria. Continued eligibility will be assessed at the Screening Visit until treatment randomization on Day 1, with the exception of criteria requiring confirmation by central reading center, which will be assessed at screening only. The Investigator will exercise medical and scientific judgement in deciding whether a laboratory finding, or other assessment, should be reassessed within the Screening period. Subjects that do not meet all the requirements as outlined in the eligibility criteria (screen failures), may be rescreened at the discretion of the Investigator.

4.2.1. Inclusion Criteria

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

1. Male or female subjects, ≥50 years of age.

2. Documented diagnosis of wAMD in the study eye, with onset of disease that began at any time prior to the Screening Visit.

3. Documented anatomical response (i.e., reduction in fluid on SD-OCT) to previous intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections in the study eye prior to the Screening Visit.

4. Previously treated with at least two anti-VEGF intravitreal injections (i.e., bevacizumab, ranibizumab, aflibercept, or faricimab) for wAMD per standard of care in the study eye within 6 months prior to the Screening Visit.

5. Received previous anti-VEGF therapy 2 to 5 weeks (14 to 35 days) in the study eye prior to Screening Visit, but no more than 42 days prior to randomization to study treatment on Day 1.

6. BCVA ETDRS letter score of 35 letters (20/200 Snellen equivalent) to 85 letters (20/20 Snellen equivalent) in the study eye at the Screening Visit and on Day 1.

7. Able to understand, and willingness to sign, the informed consent and to provide access to personal health information via Health Insurance Portability and Accountability Act (HIPAA) authorization.

8. Willingness and ability to comply with all scheduled visits, restrictions, and assessments.

9. For women of childbearing potential, or men with female partners of childbearing potential, agreement to the use of an appropriate form of contraception at the Screening Visit and for the duration of the study.

4.2.2. Exclusion Criteria

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

1. History of pars plana vitrectomy surgery, submacular surgery, or other surgical intervention for AMD in the study eye.

2. Prior treatment with Visudyne® (verteporfin), external beam radiation therapy, or transpupillary thermotherapy in the study eye.

3. Previous treatment with intravitreal corticosteroid injection or device implantation in the study eye.

4. Previous focal laser photocoagulation used for AMD treatment in the study eye.

5. Total CNV lesion size >12 disc areas (30.5 mm^2) as assessed by FA in the study eye at the Screening Visit.

6. Central subfield thickness (CST) > 350 µm in the study eye at the Screening Visit or Day 1.

7. Intraretinal cystic fluid >25 µm in diameter involving the central subfield and/or disruption of normal morphology (loss of foveal depression, disruption of external limiting membrane) secondary to cystic intraretinal fluid within the central subfield, in the study eye at Screening Visit. Diffuse (non-cystic) intraretinal fluid would not be excluded.

8. Subretinal hemorrhage in the subfoveal/juxtafoveal location and hemorrhage greater than 1 disc are (1.8 mm^2) if located less than 200 µm from the foveal center in the study eye at either the Screening Visit or Day 1.

9. Subfoveal fibrosis, atrophy, or scarring in the center subfield in the study eye at the Screening Visit.

10. Fibrosis >50% of the total lesion, in the study eye at the Screening Visit.

11. Retinal pigment epithelium detachment (RPED) thickness >400 µm at any point within 3 mm of the foveal center in the study eye at either the Screening Visit or Day 1.

12. Retinal pigment epithelial tear in the study eye at the Screening Visit or Day 1.

13. Any concurrent intraocular condition in the study eye (e.g., cataract or glaucoma) that, in the opinion of the Investigator, would either require surgical intervention during the study to prevent or treat visual loss that might result from that condition or affect interpretation of the study results.

14. Historical or active intraocular inflammation (grade trace or above) in the study eye, other than expected findings from routine cataract surgery.

15. History of vitreous hemorrhage in the study eye within 12 weeks prior to the Screening Visit.

16. History of rhegmatogenous retinal detachment or treatment for retinal detachment or macular hole (stage 3 or 4) in the study eye.

17. Aphakia or pseudophakia with the absence of the posterior capsule in the study eye (YAG capsulotomy is permitted).

18. Spherical equivalent of the refractive error in the study eye demonstrating >8 diopters of myopia.

19. For subjects who have undergone prior refractive or cataract surgery in the study eye, preoperative refractive error in the study eye exceeding 8 diopters of myopia.

20. Intraocular surgery (including cataract surgery) in the study eye within 12 weeks prior to the Screening Visit.

21. Uncontrolled ocular hypertension or glaucoma in the study eye (defined as intraocular pressure [IOP] >25 mmHg or a cup to disc ratio ≥0.8, despite treatment with 2 or more classes of antiglaucoma medication) and any such condition which the Investigator feels may require a glaucoma-filtering surgery while in the study.

22. History of glaucoma-filtering surgery, tube shunts, or microinvasive glaucoma surgery in the study eye.

23. History of corneal transplant in the study eye.

24. BCVA using ETDRS charts <30 letters (20/250 Snellen equivalent) in the fellow eye.

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

44. Inability to obtain fundus photographs, FA, fundus autofluorescence, or SD-OCT images of sufficient quality to be analyzed and graded by the central reading center.

45. Historical or active diagnosis of any medical or psychological condition that could interfere with the ability of the subject to give informed consent, or to comply with study or follow-up procedures.

46. Previous participation in any ocular or non-ocular (systemic) disease studies of investigational drugs within 30 days prior to the Screening Visit (excluding vitamins and minerals).

47. Use of anti-mitotic or anti-metabolite therapy within 30 days or 5 elimination half-lives of the Screening Visit, whichever is longer.

48. Intolerance, contraindication or hypersensitivity to topical anesthetics, dyes, povidone iodine, mydriatic medications, or any of the ingredients of the EYP-1901 insert.

49. Requirement for continuous use of any protocol-prohibited medications or treatments.

50. Pregnant or nursing females; females of childbearing potential who are unwilling or unable to use an acceptable method of contraception during the study as outlined in this protocol.

4.3. Determination of Sample Size

The primary objective of the study is to provide efficacy and safety data in a prospective, randomized, double-masked, controlled trial. Designated Sponsor/CRO individuals will be unmasked upon completion of Week 32, at which point efficacy and safety endpoints will be analyzed for all randomized subjects. However, the study is not formally powered to perform statistical hypothesis testing between each EYP-1901 arm versus aflibercept in average change in BCVA from Day 1 averaged over Week 28 and Week 32. Approximately 150 subjects will be randomized at 1:1:1 ratio to each of three treatment arms.

4.4. Treatment Assignment and Blinding

This is a randomized, double-masked, parallel study. Subjects will be assigned to the 3 different treatment arms (2,060 µg EYP-1901, 3,090 µg EYP-1901, or 2 mg [0.05 mL] aflibercept) based on the randomization code at 1:1:1 ratio. The randomization code will be generated using SAS® version 9.4 or higher 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.

Participants, 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 unmasked investigators administering the study treatments, masking will be maintained for subjects and the investigators conducting the study assessments. Sham injections will be used during the study to maintain masking of the study treatments. Only a limited number of sponsor representatives and a designated Contract Research Organization team otherwise uninvolved in the study will be unmasked at Week 32 to conduct endpoint analysis.

The masking of the study will be broken after the database has been locked. Treatment assignment for any given subject will remain masked to masked primary investigators, masked site personnel, and study subjects through study completion.

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 insert (2 inserts for 2,060 µg dose or 3 inserts for 3,090 µg dose), has been designed to deliver vorolanib into the vitreous humor for at least 9 months.

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

4.6. Study Procedures

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.

Statistical Analysis Plan for Interventional Studies
Sponsor: EyePoint Pharmaceuticals, Inc.; Protocol No.: EYP-1901-201

Table 1: Schedule of Study Procedures and Assessments for EYP-1901-201

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

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

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

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

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

a. Subjects who terminate the study prior to the Week 56 (End of Study) visit should undergo all procedures noted for the Early Termination Visit.
b. Vital signs will include pulse rate, respiratory rate, body temperature, and systolic and diastolic blood pressure (average of 3 readings will be taken in a resting state).
c. Anterior and posterior segments ocular examination.
d. Check central retinal artery perfusion following study injection.
e. At Week 8 measure IOP at 10 (+/- 5) and 60 (+/- 10) minutes following the second intravitreal injection (i.e., EYP-1901 or sham injection). If IOP measurements at any study time points are ≥30 mmHg, two additional measurements should be performed and IOP recorded as a mean of three measurements.
f. Spectral-domain – optical coherence tomography angiography (SD-OCTA) or swept-source – optical coherence tomography angiography (SS-OCTA) imaging to be collected at these time points at pre-specified study sites where SD-OCTA equipment is available.
g. Clinical laboratory testing will include hematology, serum chemistry, coagulation, and urinalysis evaluations (refer to the Study Laboratory Manual).
h. Females of childbearing potential only. Positive urine pregnancy results will be confirmed by a serum pregnancy test.
i. Pharmacokinetic analyses of vorolanib and its main metabolite will be performed on blood plasma and aqueous humor (study eye only) samples.
j. Adverse events, ocular and non-ocular, will be collected from the time the informed consent is signed. However, for safety analysis, only treatment-emergent adverse events (TEAEs) will be summarized.

5. Endpoints

5.1. Primary Efficacy Endpoint

The primary efficacy endpoint is average change in BCVA from Day 1 averaged over Week 28 and Week 32.

5.2. Secondary Efficacy Endpoints

The secondary objectives will be assessed with the following secondary endpoints:

- Change from Day 1 in BCVA up to Week 56
- Proportion of subjects with ≥5, ≥10, and ≥15 BCVA letters changes from Day 1 up to Week 56
- Proportion of subjects not receiving a supplemental injection of aflibercept in the study eye up to Week 56
- Median time to first supplemental injection of aflibercept in the study eye following the EYP-1901 dose at Week 8
- Number of aflibercept injections by Week 56
- Mean change from Day 1 in CST in microns by SD-OCT up to Week 56
- Change from Day 1 in height of subretinal fluid by SD-OCT up to Week 56
- Change from Day 1 in total lesion area by FA up to Week 56
- Change from Day 1 in total CNV area by FA up to Week 56

5.3. Pharmacokinetic Endpoints

The pharmacokinetic endpoints are:

- Systemic exposure to vorolanib measured through plasma levels up to Week 56
- Ocular exposure to vorolanib measured through aqueous levels up to Week 32

5.4. Safety Endpoints

The safety endpoints are:

- Rates of ocular (study eye and non-study eye) and non-ocular TEAEs up to Week 56
- Change from Day 1 in proportion of subjects with no detectable intraretinal fluid/cysts in the central subfield up to Week 56

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 were randomized into the study and received at least one dose of study treatment (defined as the Day 1 dose for the aflibercept arm or both Week 8 doses for each EYP-1901 arm). 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 Analysis Set

The Per-protocol (PP) Analysis Set will include all subjects who received at least one dose of study treatment (aflibercept or EYP-1901, see FAS definition), continue until at least Week 32 (i.e., have had the primary endpoint assessed, that is, have a Week 28 and/or Week 32 BCVA in the study eye), 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 analyses.

6.4. Safety Set

The Safety Set will include all subjects who received at least one dose of study treatment. Subjects will be assigned according to the treatment actually received. Safety set will be used to summarize treatment exposure and safety data.

6.5. Pharmacokinetic Set

The Pharmacokinetic (PK) Set will include all participants in the Safety Set for whom at least one evaluable plasma or aqueous humor (AH) PK sample is available.

7. Estimands

No estimands were defined within the protocol of this exploratory 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 one 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, and maximum.
- Categorical variables will be summarized using number of subjects (n) and frequency 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 the first dose of 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.

A rescue injection, or “supplemental injection”, is any unscheduled injection of aflibercept, whether or not a subject has met rescue criteria. For the aflibercept arm, any aflibercept injection following Week 8 which does not occur at Weeks 16, 24, 32, 40, 48, or 56, is a “supplemental” injection. For either of the EYP-1901 arms, any aflibercept injection following the Week 8 visit is a “supplemental” injection.

8.3. Missing Data

8.3.1. Procedure Dates

A partial/missing date recorded on the Procedures CRF will be handled as follows:

- If only the day is missing, and the month and year match the month and year of the first dose date, then the day of the first dose 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 first dose date, then the month and the day of the first dose date will be imputed. Otherwise, 01 January will be used.

- If the date is completely missing, the first dose date will be imputed.

8.3.2. Medication Dates

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

- If only the day is missing, and the month and year match the month and year of the first dose date, then the day of the first dose 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 first dose date, then the month and the day of the first dose date will be imputed. Otherwise, 01 January will be used.
- If the start date is completely missing, the first dose date will be imputed, unless the stop date is prior to the first dose 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 last dose date will be used.

8.3.3. 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 the first dose, 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 first dose, 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	Acceptable Window	Visit Windows for Analysis
Screening	-21 to -7	NA	
Day 1	1	N/A	
Week 4	28	± 5 days	Study Days 2 to 42
Week 8	56	± 5 days	Study Days 43 to 70
Week 12	84	± 5 days	Study Days 71 to 98
Week 16	112	± 5 days	Study Days 99 to 126
Week 20	140	± 5 days	Study Days 127 to 154
Week 24	168	± 5 days	Study Days 155 to 182
Week 28	196	± 5 days	Study Days 183 to 210
Week 32	224	± 5 days	Study Days 211 to 238
Week 36	252	± 5 days	Study Days 239 to 266
Week 40	280	± 5 days	Study Days 267 to 294
Week 44	308	± 5 days	Study Days 295 to 322
Week 48	336	± 5 days	Study Days 323 to 350
Week 52	364	± 5 days	Study Days 351 to 378
Week 56	392	± 5 days	Study Days 379 to 406
Withdrawal	Study discontinuation	N/A	

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 Fluorescein Angiography

Visit	Target Study Day	Acceptable Window	Visit Windows for Analysis
Screening	-21 to -7	NA	
Week 32	224	± 5 days	Study Days 1 (post-dose) to 308
Week 56	392	± 5 days	Study Days 309 to 406

Table 4: Visit Windows for Plasma PK and Clinical Laboratory Data

Visit	Target Study Day	Acceptable Window	Visit Windows for Analysis
Screening	-21 to -7	NA	
Week 8	56	± 5 days	Study Days 1 (post-dose) to 98
Week 20	140	± 5 days	Study Days 99 to 182
Week 32	224	± 5 days	Study Days 183 to 266
Week 44	308	± 5 days	Study Days 267 to 350
Week 56	392	± 5 days	Study Days 351 to 406

Table 5: Visit Windows for Aqueous PK

Visit	Target Study Day	Acceptable Window	Visit Windows for Analysis
Screening	-21 to -7	NA	
Week 8	56	± 5 days	Study Days 1 (post-dose) to 98
Week 20	140	± 5 days	Study Days 99 to 182
Week 32	224	± 5 days	Study Days 183 to 406

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 one windowed record is available, the record closest to the target study day will be used for analysis.
    - If two windowed records are equidistant from the target study day, the windowed record after the target study day will be used.

Electrocardiogram (12-lead) data will be summarized at baseline and Week 56 / end of treatment.

8.5. Pooling of Centers

No by-center analyses are planned.

8.6. Subgroups

Planned sub-group analyses are detailed in Section 10.

8.7. Multiple Comparisons and Multiplicity

Not applicable.

8.8. Adjustment for Covariates

The primary and secondary efficacy endpoints will include baseline score as a covariate, when applicable.

8.9. Interim Analyses

No interim analyses are planned for this study. There will be an unmasked analysis of the primary efficacy endpoint (average change in BCVA from Day 1 averaged over Week 28 and Week 32) once all subjects have completed Week 32 or discontinued prior to Week 32. Designated Sponsor/CRO individuals will be unmasked at this point in the study; this primary efficacy endpoint readout will be prepared by an unmasked statistical team who are otherwise uninvolved in the study (prior to full database lock) and will be distributed to only a limited number of sponsor representatives. Details of the primary efficacy endpoint readout will be added to this SAP once scope is confirmed.

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 (for treated subjects) and overall to include the following:

- Number of subjects screened
- Number of screen failure subjects and reason for screen failure (inclusion and/or exclusion criteria violation)
- Number of subjects randomized
- Number (%) of subjects in the Full Analysis Set, Per-protocol Analysis Set, Safety Set, and Pharmacokinetic Set
- 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 will be listed by subject.

Major protocol deviations will be summarized by treatment and overall for the Full Analysis Set using frequency counts and percentages.

9.3. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the Full Analysis Set by treatment and overall. The following demographic variables will be listed and summarized:

- Age in years at screening

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

  floor(YRDIF(<date of birth variable>, screen date, "AGE"))

- Age category (≤65 years, >65 years)
- Sex (Male, Female)

- Child-bearing potential (Yes, No). If child bearing potential is answered ”No”, then reason will be summarized (Surgically sterile, Post-menopausal)
- 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, Not Reported)
- Study Eye (OD, OS)

The following baseline characteristics will be listed and summarized for the study eye:

- BCVA score (letter)
- BCVA score categories (<=55 letters, 56 – 70 letters, >=71 letters)
- Central subfield thickness (µm)
- Central subfield thickness categories (<=300 µm, >300 µm)
- Years since diagnosis of AMD in study eye
- Number of anti-VEGF injections received in study eye 12 months prior to screening visit

Diagnosis of AMD will be identified from the collected medical history data as those events with preferred term of “Neovascular age-related macular degeneration” or “wet age-related macular degeneration”. For each subject, the earliest start date associated with this preferred term in the study eye will be the first diagnosis date of AMD in the study eye, and the years since diagnosis of AMD in the study eye will be computed as (date of first administration of study treatment – start date of AMD in the study eye + 1) / 365.25 days per year. In the event of an incomplete AMD start date, the following algorithm will be used to impute an AMD start date for the purpose of computing years since diagnosis.

- Known year, unknown month and day (or known year and day, unknown month): January 1 of the year will be imputed.
- Known year and month, unknown day: The first day of the month will be imputed.

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 number of subjects in respective population.

9.4. Medical History

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

9.5. Prior and Concomitant Medications

Medications will be coded using the most recent version of the World Health Organization Drug Dictionary (Global B3 March 2022 Version). Missing medication dates will be handled as described in Section 8.3.2 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 medications are defined as all medications recorded on the “Concomitant Medications” CRF taken prior to Day 1, whether ongoing or not. Concomitant medications are defined as medications that are ongoing at the start of study treatment or started on or after the first dose of study treatment; if the medication is ongoing, it is considered to be concomitant.

The number and percentage of participants by treatment and overall in the Safety Set for prior medication (ocular study-eye, ocular non-study eye, and non-ocular) and concomitant medication (ocular study-eye, ocular non-study eye, and non-ocular) will be summarized by Anatomical Therapeutic Chemical (ATC) Level 2 and ATC Level 4. They will be presented by descending overall frequency of ATC Level 2 Term and within each ATC Level 2 Term, by descending overall frequency of ATC Level 4. Subjects will be counted only once for each ATC Level 2 and ATC Level 4 if they have multiple records of the same ATC Level 2 or ATC Level 4 terms in the database. The ATC Level 1 term will be used for summarization when no coding is available for ATC Levels 2 through 4.

9.6. Prior and Concomitant Procedures

Procedures will be coded using MedDRA version 25.0. Missing procedure dates will be handled as described in Section 8.3.1.

Procedures dates from the eCRF will be used to determine whether the procedure is prior or concomitant. Prior procedures are defined as all procedures recorded on the “Concomitant Procedures” CRF which occur prior to Day 1. Concomitant procedures are defined as procedures that occur on or after the date of first dose of study treatment.

The number and percentage of participants by treatment and overall in the Safety Set for prior procedures (ocular study-eye, ocular non-study eye, and non-ocular) and concomitant procedures (ocular study-eye, ocular non-study eye, and non-ocular) will be summarized by system organ class and preferred term. They will be presented by descending overall frequency of system organ class and within each system organ class, by descending overall frequency of preferred term. Subjects will be counted only once for each system organ class and preferred term if they have multiple records of the same system organ class or preferred term in the database.

9.7. Extent of Exposure

Exposure to study treatment will be defined in the following ways and summarized descriptively by treatment group and overall for the Safety Set:

- Number of scheduled aflibercept injections administered (for the aflibercept arm) and number of scheduled EYP-1901 injections administered (for the EYP-1901 arms).

- The number and percentage of subjects who receive an aflibercept injection at each visit (including visits at which no injection was scheduled but at which rescue injection was received), for which the denominator will be all Safety Set subjects who did attend the visit in question. At Week 8, the number and percentage of subjects who receive Injection 1 (aflibercept) and Injection 2 (EYP-1901 or sham), separately, will be summarized. Apart from Injection 2 at Week 8, sham injections will not be summarized as injections received.

10. Efficacy

All efficacy endpoints will be summarized descriptively by treatment group and for EYP-1901 overall. For continuous endpoints, number of subjects (n), mean, standard deviation (SD), median, minimum (min), and maximum (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.

The unit of analysis in this study is the study eye for all ocular efficacy endpoints. All efficacy analyses will use a 2-sided alpha at 0.05 level of significance and corresponding 80%, 85%, 90%, 95%, and 97.5% CIs will be presented where applicable. No adjustments for multiple comparisons will be implemented for the analysis of any primary or secondary endpoint.

10.1. Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is change from baseline averaged over Week 28 and Week 32 in BCVA in study eye and will be evaluated using the Full Analysis Set. CCI

[redacted]

Sensitivity Analysis

The following sensitivity analyses will be conducted for the primary endpoint. As applicable, data missing after subject withdrawal due to lack of efficacy or adverse event related to study treatment will be considered missing not at random (MNAR); all other missing data will be considered missing at random (MAR).

- The main analysis for the primary parameter will be repeated for the Per Protocol Analysis Set.

- For FAS subjects having missing BCVA data in the study eye at Week 28 and Week 32, a last observation carried forward (LOCF) approach will be used to impute a value for the missing Week 28/32 average, and the primary endpoint with the imputed data will be analyzed using analysis of covariance with change from baseline to the Week 28/32 average BCVA as the response variable, treatment as a factor, and baseline BCVA as a covariate.
- For FAS subjects having missing BCVA data at any visit, multiple imputation (50 iterations) using treatment-based regression methodology will be used to impute all missing data (missing at random [MAR] or missing not at random [MNAR]) and then the change from baseline for the resulting Week 28/32 average values will be analyzed using analysis of covariance with change from baseline to the Week 28/32 average BCVA as the response variable, treatment as a factor, and baseline BCVA as a covariate.
- For FAS subjects having missing BCVA data at any visit, MNAR data (data missing following early withdrawal due to lack of efficacy or adverse event related to study treatment) will be multiply imputed (50 iterations) based on the worst half of the subjects who have completed the study within the same treatment group, and MAR data (all other missing data) will be imputed via LOCF. Change from baseline for the resulting Week 28/32 average values will be analyzed using analysis of covariance with change from baseline to the Week 28/32 average BCVA as the response variable, treatment as a factor, and baseline BCVA as a covariate.
- For FAS subjects having missing BCVA data in the study eye at Week 28 and Week 32, MAR data will be imputed using LOCF, and MNAR data will be singly imputed using the baseline observation carried forward, and the primary endpoint with the imputed data will be analyzed using analysis of covariance with change from baseline to the Week 28/32 average BCVA as the response variable, treatment as a factor, and baseline BCVA as a covariate.
- Further sensitivity analysis will be conducted for FAS, applying similar methodology to that used for the main analysis of the primary efficacy endpoint, for the change from Week 8 assessment averaged over Week 28 and Week 32 in BCVA in the study eye. Week 8 assessment will be the last non-missing assessment prior to the Week 8 study treatment.

Exploratory Analysis

Observed percent fibrosis values (from fluorescein angiography) and change from baseline to each follow-up visit (and the average of Weeks 28 and 32) will be summarized descriptively for FAS. An assessment will be made of the correlation between observed values and change from baseline in percent fibrosis and the change from baseline in BCVA at each follow-up visit, summarized using Pearson's correlation coefficient with a p-value assessing the significance of the correlation under a null hypothesis of zero correlation.

Sub-group Analysis

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

- Age at screening (> median, <= median)
- Sex (male, female)
- Baseline BCVA ETDRS letter score in the study eye (three separate sub-group categorizations)

- (<= median, > median)
- (<= 58 letters, > 58 letters)
- (<= 80 letters, > 80 letters)

- Baseline CST in study eye (<=300 µm, >300 µm)
- Baseline retinal pigment epithelial detachment (RPED) size (<= 300 µm, > 300 µm)
- Baseline iris pigmentation of study eye (blue, brown, green, grey, amber, hazel, red, other)
- Number of anti-VEGF injections in the study eye in 12 months prior to screening (two separate sub-group categorizations)
  - (<= median, > median)
  - (<= 2 injections, > 2 injections)
- Number of supplemental aflibercept/anti-VEGF injections after and excluding Week 8 in the study eye (five separate sub-group categorizations)
  - (<= 3 injections, > 3 injections)
  - (<= 2 injections, > 2 injections)
  - (<= 1 injection, > 1 injection)
  - (0 injections, > 0 injections)
  - (0 to 1 injection, 2 to 3 injections, 4 or more injections)
- Type of prior anti-VEGF in study eye 12 months prior to screening visit (i.e., aflibercept, ranibizumab, faricimab, or bevacizumab)
- Number of unique prior anti-VEGF in study eye 12 months prior to screening visit
- Time since diagnosis in months at Screening (three separate sub-group categorizations)
  - (<= median, > median)
  - (<= 9 months, > 9 months)
  - (<= 48 months, > 48 months)
- Type of choroidal neovascularization (CNV) in study eye per OCT at Screening (different types will be used as sub-groups)
- Baseline Intraretinal Fluid in study eye
  - Absent vs present

10.2. Secondary Efficacy Endpoint(s) Analyses

The FAS summarization and main analysis performed for the primary endpoint (Section 10.1) will be repeated for the following secondary efficacy endpoints. No plots will be prepared, except as noted.

- Change from baseline in BCVA in study eye up to Week 56
- Change from baseline in CST (microns) by SD-OCT in study eye up to Week 56 (line plots of model-based LS Means and standard errors over time will be prepared); percent change will also

be summarized and analyzed. Summarization and analysis will be performed for centrally read CST and site reported CST, for the study eye and non-study eye.

- Summarization and analyses (not plots) will be generated for the following subgroups as defined in Section 10.1.
  - Number of supplemental aflibercept/anti-VEGF injections in the study eye (five separate sub-group categorizations)

- Change from baseline in height of subretinal fluid by SD-OCT in study eye up to Week 56; summarization and analysis will be performed for centrally read data for both the study eye and non-study eye.
- Change from baseline in total lesion area by FA in study eye up to Week 56
- Change from baseline in total CNV area by FA in study eye up to Week 56; summarization and analysis will be performed for centrally read data for both the study eye and non-study eye.

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- Proportion of subjects with ≥5 BCVA letter gain in the study eye from baseline up to Week 56
- Proportion of subjects with ≥5 BCVA letter loss in the study eye from baseline up to Week 56
- Proportion of subjects with ≥10 BCVA letter gain in the study eye from baseline up to Week 56
- Proportion of subjects with ≥10 BCVA letter loss in the study eye from baseline up to Week 56
- Proportion of subjects with ≥15 BCVA letter gain in the study eye from baseline up to Week 56
- Proportion of subjects with ≥15 BCVA letter loss in the study eye from baseline up to Week 56
- Proportion of subjects not receiving a supplemental injection of aflibercept in the study eye up to Week 56 (this will be summarized at each visit as the number and percent of subjects not receiving a supplemental injection at the visit, and cumulatively as the number and percent of subjects not receiving a supplemental injection any time prior to the visit with a corresponding bar chart)
- Proportion of subjects with no detectable intraretinal fluid/cysts in the central subfield of the study eye up to Week 56

The cumulative number of supplemental aflibercept injections since Week 8 through Week 32, up to (but not including) Week 32, through Week 56, and up to (but not including) Week 56, normalized for the number of months on study since Week 8, will be computed as (number of supplemental aflibercept injections received since Week 8) / (time within study period in months), multiplied by 6 months (Week 32) or 12 months (Week 56), where time within a study period in months equals (date of period completion or early discontinuation from study – date of Week 8 visit + 1) / 30.4375; the date of period completion or study discontinuation is the date of the visit ending the given period, or the date one day prior to the visit ending the period when the visit is not included in the given period. The number and percent of subjects needing any supplemental aflibercept injection (not including loading doses) and each normalized number

of supplemental aflibercept injections will be summarized descriptively for the FAS. Note that normalized counts will be computed only for subjects who made it to the Week 8 visit, and subjects may have 0 supplemental aflibercept injections. Mean number of supplemental aflibercept injections will be compared between each EYP-1901 treatment group and the aflibercept treatment group using a t-test, or the Mann Whitney U Range test if the data are not normally distributed. The cumulative number of aflibercept injections in total (planned plus supplemental) since Week 8 through Week 32, up to (but not including) Week 32, through Week 56, and up to (but not including) Week 56, normalized for the number of months on study since Week 8, will be computed and summarized in a similar manner.

The cumulative number of supplemental aflibercept injections including loading doses through Week 32, up to (but not including) Week 32, through Week 56, and up to (but not including) Week 56, normalized for the number of months on study, will be computed as (number of supplemental aflibercept injections received since first loading dose of aflibercept) / (time within study period in months), multiplied by 6 months (Week 32) or 12 months (Week 56), where time within a study period in months equals (date of period completion or early discontinuation from study – date of first loading dose of aflibercept + 1) / 30.4375; the date of period completion or study discontinuation is the date of the visit ending the given period, or the date one day prior to the visit ending the period when the visit is not included in the given period. Each normalized number of supplemental aflibercept injections including loading doses will be summarized descriptively for the Full Analysis Set. Mean number of supplemental aflibercept injections will be compared between each EYP-1901 treatment group and the aflibercept treatment group using a t-test, or the Mann Whitney U Range test if the data are not normally distributed. The cumulative number of aflibercept injections in total (planned plus supplemental) including loading doses through Week 32, up to (but not including) Week 32, through Week 56, and up to (but not including) Week 56, normalized for the number of months on study, will be computed and summarized in a similar manner.

Treatment burden in the study eye (injections per month) will be calculated for each subject for the pre-injection period and for the periods from Week 8 (excluding loading dose at Week 8) through Week 32 and Week 8 (excluding loading dose at Week 8) through Week 56. The pre-injection period will be defined as 12 months prior to the actual screening visit for subjects whose first ever anti-VEGF injection was more than 12 months prior to screening, and will be defined as the first ever anti-VEGF injection prior to screening to the actual screening visit for subjects whose first ever anti-VEGF injection was within 12 months of screening. During a particular period (pre-injection, Week 8 [excluding loading dose at Week 8] through Week 32, and Week 8 [excluding loading dose at Week 8] through Week 56), the treatment burden will be calculated for each subject as the number of injections received in the study eye (any anti-VEGF injection during the pre-injection period [see Section 9.5 regarding identification of anti-VEGF medications], and any scheduled or supplemental aflibercept injection during an on-study period) divided by the number of months over which the subject was observed during the period. Percent change will be calculated for each subject as the follow-up period treatment burden minus the pre-injection treatment burden, divided by the pre-injection treatment burden, times 100. Treatment burden during each period and percent change in treatment burden from the pre-injection period for each follow-up period will be summarized descriptively. CCI [redacted]

Treatment burden will also be normalized to 6 and 12 months, as follows, and summarized in a similar manner.

- Treatment burden will be normalized to 6 months for a 6-month pre-injection period (defined similarly to the 12-month pre-injection period) and the Week 8 (excluding the loading dose at Week 8) to Week 32 on-study period.

- The treatment burden from the originally defined pre-injection period and Week 8 (excluding loading dose at Week 8) through Week 56 on-study period will be normalized to 12 months.

Swim lane plots corresponding to the treatment burden summarization will be prepared for the Week 8 through Week 32 period and the Week 8 through Week 56 period. Each plot will show for each subject the occurrence of anti-VEGF injections in the 12 months preceding screening in the current study according to actual time, and for each scheduled visit in the follow-up period of interest will show the occurrence of supplemental injection in the study eye, no supplemental injection, or missed visit. Subjects will be grouped by treatment. The mean percent change in treatment burden will be displayed for each treatment.

Time to first supplemental aflibercept injection (weeks) in the study eye following study treatment (EYP-1901 or aflibercept) administration at Week 8 will be computed, only for subjects receiving study treatment administration at Week 8, as the date of the first supplemental aflibercept injection minus the date of the Week 8 study treatment administration, divided by 7 days per week; subjects not receiving any supplemental aflibercept injection following study treatment administration at Week 8 will be censored at their date of last visit (those who completed) or date of last contact (those who discontinued the study early). The time to first supplemental aflibercept injection in the study eye following study treatment administration at Week 8 will be summarized for the Full Analysis Set by treatment group with the number of subjects treated at Week 8, number and percentage of subject treated at Week 8 who received supplemental aflibercept, number and percentage of subjects treated at Week 8 who were censored, and Kaplan-Meier estimates of median and first and third quartiles. The EYP-1901 treatment groups will be compared to the aflibercept group using a log-rank test. A corresponding Kaplan-Meier plot will be prepared.

FAS subjects who have been assessed for the need for supplemental aflibercept injections will be classified as under rescued, over rescued, and/or correctly rescued, as follows. Note, a subject can be classified into more than one rescue use category, since subjects can be assessed for the need for supplemental injections more than once.

- Under rescued: A subject will be classified as under rescued if they did meet the protocol specified supplemental injection criteria but did not receive a supplemental injection at the time of the assessment of supplemental injection criteria.

- Over rescued: A subject will be classified as over rescued if they did not meet the protocol specified supplemental injection criteria but did receive a supplemental injection at the time of the assessment of supplemental injection criteria.

- Correctly rescued: A subject will be classified as correctly rescued if they did meet the protocol specified supplemental injection criteria and did receive a supplemental injection at the time of the assessment of supplemental injection criteria.

The number and percentage of FAS subjects who were assessed for the need for supplemental injection who are over rescued, under rescued, and correctly rescued will be summarized by treatment and EYP-1901 overall, for the period from baseline to Week 32 and the period from baseline to Week 56.

11. Safety

The population used for safety analyses will be the Safety Set. Safety assessments will include the incidence and severity of TEAEs, clinical laboratory evaluations (hematology, chemistry, coagulation, and urinalysis), vital sign measurements, ECGs, intraocular pressure measurements, and safety data collected from ocular examinations.

Subjects will be summarized according to treatment actually received at Week 8, aflibercept, EYP-1901 2060 µg, or EYP-1901 3090 µg. In the event a subject is randomized to an EYP-1901 arm and during the EYP-1901 injection receives only 1 insert, they will be summarized according to their randomized dose and documented appropriately in output footnotes.

11.1. Adverse Events

All AEs will be coded using MedDRA version 25.0 and will be presented in the following data listings by SOC and PT for each subject.

- All AEs
- AEs related to study treatment
- Serious adverse events (SAEs)
- SAEs related to study treatment
- All deaths
- AEs leading to study treatment discontinuation
- AEs leading to study withdrawal

Treatment-emergent adverse events (TEAEs) are AEs that occur after the first dose of study treatment administration. Sensitivity analyses (overall TEAE summaries only) will be done for treatment-emergent adverse events that start on or after Day 1 for the aflibercept arm and on or after Week 8 for the EYP-1901 arms, and again for treatment-emergent adverse events that start on or after Week 8 for all treatment groups. Missing/incomplete start or stop date associated with an adverse events (AEs) will be handled as per Section 8.3.3 to determine whether an AE is a TEAE. The following categories of TEAEs will be summarized by treatment group and for EYP-1901 overall for the Safety Set using frequency 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 (overall, study drug related, and injection related)
- 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], fatal [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 frequency of SOC and then, within a SOC, by overall descending frequency 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 one TEAE.

Summaries of TEAEs (ocular in study eye, ocular in non-study eye, and non-ocular) by PT only will be presented by treatment group and EYP-1901 overall, sorted by overall descending frequency 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), chemistry, and urinalysis results (raw and change from baseline) will be summarized by actual treatment group and for EYP-1901 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 participants 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, respiratory 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 per minute), body temperature [°C], and respiratory rate [breaths per minute]) and changes from baseline will be summarized by scheduled visit and by treatment group and for EYP-1901 overall for the Safety Set.

Potentially clinically significant values will be identified for vital sign parameters as outlined in Table 4. For any post-baseline scheduled visit, potentially clinically significant values will be summarized by treatment group and visit. Any vital sign results considered clinically significant by the investigator will be captured as adverse events.

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

Table 4: 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. ECG

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 group and for EYP-1901 overall for the Safety Set.

In addition, the number and percentage of participants with PCS and potentially clinically significant change (PCSC) values will be summarized by scheduled visit and for any time post-baseline. Potentially clinically significant 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 following categories: 'Normal', 'Abnormal, Not Clinically Significant', and 'Abnormal, Clinically Significant'. The shift table will be presented by visit, treatment group, and EYP-1901 overall.

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

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 (IOP)

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

For IOP, the observed value at each scheduled visit and change from baseline at each scheduled visit will be summarized descriptively by treatment group and for EYP-1901 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.

A shift table of overall IOP interpretation from baseline to scheduled post-baseline visits will be presented for the following categories: 'Normal', 'Abnormal NCS', and 'Abnormal CS'. The shift table will be presented by visit and by treatment group and EYP-1901 overall, for both the study eye and non-study eye. The IOP parameter will also be listed by participant.

11.6. Ocular Examinations

The observed values of ocular examination parameters at each scheduled visit will be summarized by treatment group and for EYP-1901 overall for the Safety Set for study eye and non-study eye. The ocular examination parameters will also be listed by participant.

The vitreous haze grading scale from the dilated ophthalmoscopy ocular examination is as follows, with higher scores indicating a worse result.

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

The anterior chamber cell grading scale from the slit lamp biomicroscopy ocular examination is as follows, with higher scores indicating more cells.

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

The centrally read values of central retinal lesion thickness obtained by SD-OCT and the change from baseline at each follow-up visit will be summarized by treatment group and for EYP-1901 overall for the Safety Set for the study eye and non-study eye.

Centrally read subretinal hyperreflective material (SHRM) data will be summarized by treatment group and for EYP-1901 overall for the Safety Set for the study eye and non-study eye. Data summarized will include SHRM presence (absent, present by location), SHRM manually measured greatest height (observed values at each visit and change from baseline at each follow-up visit).

Centrally read pigment epithelial detachment (PED) data will be summarized by treatment group and for EYP-1901 overall for the Safety Set for the study eye and non-study eye. Data summarized will include

PED presence (none, present by location), manually measured tallest PED (observed values at each visit and change from baseline at each follow-up visit).

Centrally read intraretinal fluid data will be summarized by treatment group and for EYP-1901 overall for the Safety Set for the study eye and non-study eye. The number and percentage of participants with shift changes from baseline (present, absent, cannot determine) to each scheduled follow-up visit (increased, decreased, stable, resolved, cannot determine) will be tabulated.

11.7. Intraretinal Fluid/Cysts

The number and percentage of participants with no detectable intraretinal fluid/cysts in the central subfield will be summarized by scheduled visit and for any time post-baseline visits. The summary will be provided by treatment group and for EYP-1901 overall for the Safety Set, for study eye and non-study eye. Intraretinal fluid is assessed for the categories ‘Absent’, ‘Present NCS’, ‘Present CS’ and ‘Not Done’. If Intraretinal fluid assessment at any scheduled visit falls under the category ‘Absent or Present NCS’, then it will be considered as no detectable intraretinal fluid in that scheduled visit.

11.8. BCVA ETDRS Letter Score in Non-study Eye

Observed BCVA ETDRS letter score values in the non-study eye and change from baseline to each follow-up visit will be summarized descriptively by treatment group and for EYP-1901 groups overall for the Safety Set.

11.9. Centrally Read Central Subfield Thickness in Non-study Eye

Observed centrally read central subfield thickness values in the non-study eye and change from baseline to each follow-up visit will be summarized descriptively by treatment group and for EYP-1901 groups overall for the Safety Set.

11.10. Centrally Read Height of Sub-retinal Fluid in Non-study Eye

Observed centrally read height of sub-retinal fluid values in the non-study eye and change from baseline to each follow-up visit will be summarized descriptively by treatment group and for EYP-1901 groups overall for the Safety Set.

11.11. Centrally Read Total Choroidal Neovascularization Area in Non-study Eye

Observed centrally read total choroidal neovascularization area values in the non-study eye and change from baseline to each follow-up visit will be summarized descriptively by treatment group and for EYP-1901 groups overall for the Safety Set.

12. Pharmacokinetics

12.1. Pharmacokinetic Sampling

The plasma samples will be collected at Weeks 8, 20, 32, 44, and 56, and any early termination visit, and aqueous humor (study eye only) samples will be collected at Weeks 8, 20, and 32, and any early termination visit.

12.2. Data Presentation

The clinical pharmacology endpoints of this study are systemic exposure to vorolanib measured through plasma levels up to Week 56, and ocular exposure to vorolanib measured through aqueous humor levels up to Week 32.

Plasma and aqueous humor study drug concentration data will be listed. Descriptive statistics of plasma and aqueous humor PK concentrations by treatment will be presented for the PK Set; when calculating drug concentration descriptive statistics, values below the limit of quantification (BLQ) will be considered zero. The following plots 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 participant plasma concentrations versus actual time points by dose level
- Linear and log-linear scale of mean (SD) aqueous humor concentrations versus scheduled time points
- Linear and log-linear scale spaghetti plots of individual participant aqueous humor concentrations versus actual time points by dose level

13. Interim Analyses

No masked or unmasked interim analyses are planned for this study.

An unmasked analysis of the primary efficacy endpoint will take place at Week 32 prior to the end of the study once all subjects have completed Week 32 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

There are no changes from the analyses planned in the protocol.

15. Reference List

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.

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

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., cm2, Cmax) 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-1901-201
- 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
Analysis Population

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 group 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.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group 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 treatments 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 groups 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 (0.0).

- 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 is 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 one decimal place, in parentheses with no spaces, one 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 group 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 group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC 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 group (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 one 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 system organ class) has to be split over more than one 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 groups 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 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 six 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
  Listing source: Listing 16.2.4.1.1, Listing 16.2.4.1.2, Listing 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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There are no appendices.

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