Statistical Analysis Plan

For

A Phase I/II Trial for Intravitreous Treatment of Severe Ocular von Hippel-Lindau Disease Using a Combination of the PDGF Antagonist E10030 and the VEGF Antagonist Ranibizumab

Version 1.0

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TABLE OF CONTENTS

TABLE OF CONTENTS (CONTINUED)

LIST OF TABLES

1.0 INTRODUCTION

This statistical analysis plan (SAP) provides the proposed analyses for ER-VHL protocol titled "A Phase I/II Trial for Intravitreous Treatment of Severe Ocular Von Hippel-Lindau Disease Using a Combination of the PDGF Antagonist E10030 and the VEGF Antagonist Ranibizumab". This document contains eleven sections: (1) background of the study (2) data sources for analyses, (3) an overview of the study design, (4) statistical considerations, (5) baseline and protocol compliance summaries, (6) statistical analysis for the primary outcome, (7) statistical analyses for secondary outcomes, (8) review of safety analyses, (9) quality assurance plan, (10) references, and (11) mock shells. This document is based on version 5.0 of the protocol dated October 2, 2017.

1.1 VHL Disease

Von Hippel-Lindau (VHL) disease is an autosomal dominant heritable disorder in which multiple benign and malignant neoplasms and cysts of specific histopathologies develop in the kidney, adrenal gland, pancreas, brain, spinal cord, eye, inner ear, epididymis and broad ligament. The disease affects about 7,000 individuals in the United States. Retinal capillary hemangiomas (RCH) are the most common and often the earliest manifestation of VHL disease and may lead to significant vision loss. In some such eyes, inexorable progression of RCH leads to blindness and phthisis bulbi despite aggressive treatment. Levels of vascular endothelial growth factor (VEGF), a potent mediator of angiogenesis and vascular permeability, have been shown to be elevated in multiple cell types deficient in the VHL protein (pVHL). Platelet-derived growth factor (PDGF), which has an important role in stabilization of immature new vessels during angiogenesis, is upregulated in pVHL-defective cell lines and expressed in other pVHL-defective tumors. Anti-VEGF therapy alone had no beneficial effect on ocular VHL disease in two previous phase 1 studies. The objective of this study is to investigate the safety and possible efficacy of combination investigational treatment with serial intravitreal injections of E10030, a PDGF-B antagonist, and ranibizumab, a VEGF-A antagonist, in participants with severe ocular VHL disease.

2.0 DATA SOURCE

Most of the data are collected using National Eye Institute's (NEI) electronic data capture system (Electronic Medical Record [EMR]) and stored in EMR, the Clinical Research Information System (CRIS) and the Coordinating Center's secure database. Additional outcome data not captured in EMR will be provided to the Coordinating Center in Excel spreadsheet or other formats as applicable. All individual data will remain confidential.

3.0 GENERAL REVIEW OF STUDY DESIGN

3.1 Study Design

The ER-VHL study is a phase I/II, single-center, prospective, open label, non-randomized, uncontrolled, single group trial investigating the safety and potential efficacy of combined treatment of severe ocular VHL disease with serial intravitreal injections of E10030 and ranibizumab.

The study will require a minimum of 14 visits (baseline and Weeks 4, 8, 12, 16, 24, 32, 40, 48, 52, 60, 72, 84 and 104). All visits must be conducted within a window of ± seven days from the target day through Week 52 and ± 30 days thereafter. Prior to treatment at each visit, the participant will undergo an AE assessment, concomitant medication review, vital sign check and ophthalmic evaluation.

A single study eye in each participant will receive combination treatment consisting of intravitreal injections of E10030 (1.5 mg in 0.05 mL) and ranibizumab (0.5 mg in 0.05 mL) (given as separate injections during the same procedure, meaning that participants will receive two intravitreal injections per visit) every four weeks from baseline through Week 16 (totaling five treatments) and then every eight weeks through Week 48 (totaling nine treatments from baseline). The primary endpoint will be assessed by tabulation of AEs reported through Week 52. Starting after Week 52, participants may return for additional visits in the second year of the trial, as often as every 4 weeks, for evaluation and for administration of standard of care therapies, at investigator discretion; all participants will be seen at Weeks 60, 72, 84 and 104. No further administration of investigational product will occur after the Week 48 visit.

Participants will be monitored at each visit for injection-related complications such as endophthalmitis, retinal tear/detachment, intraocular hemorrhage, cataract and glaucoma and for any progression of ocular VHL disease; participants who develop such complications may be discontinued from receiving the combination treatment. They will also be monitored at each visit for intraocular inflammation (as assessed by presence of anterior chamber or vitreous cell on ophthalmoscopy).

Concomitant therapies for non-ocular conditions are allowed without restriction. If systemic treatment with either anti-VEGF or anti-PDGF therapy is required, interruption or discontinuation of combination investigational treatment will be considered and discussed with other treating physicians. Any participant who discontinue study treatment will be asked to return for all future study visits.

Standard care therapies for VHL disease, including laser photocoagulation, cryotherapy, photodynamic therapy, surgery, ocular radiation and any medication use associated with these treatments (such as use of systemic corticosteroids to minimize exudation from RCH undergoing ablative treatment) will be considered for significant clinical worsening at any time during the study, for clinical improvement at any time starting at Week 16 (as in a case where clinical improvement makes an eye more amenable to ablative or surgical treatment), and without restriction starting at Week 40 (in anticipation of unavailability of investigational product after Week 48).

3.2 Study Objective

The objective of this study is to investigate the safety and possible efficacy of combination investigational treatment with serial intravitreal injections of E10030, a PDGF-B antagonist and ranibizumab, a VEGF-A antagonist, in participants with severe ocular VHL disease.

3.3 Study Population

Three participants with severe ocular VHL disease who meet the eligibility criteria will receive the combination investigational treatment in one eye and will be followed for 104 weeks. Inclusion and exclusion criteria are listed below.

3.3.1 Inclusion Criteria

1. Participant must understand and sign the informed consent.
2. Participant must be 18 years of age or older.
3. Participant must have a diagnosis of VHL disease. In accordance with established criteria for diagnosis,[1,2] any one of the following will be considered sufficient evidence that VHL disease is present:
    - A family history of VHL disease plus one or more of the following lesions: RCH, spinal or cerebellar hemangioblastoma, pheochromocytoma, multiple pancreatic cysts, epididymal or broad ligament cystadenomas, multiple renal cysts or renal cell carcinoma before age 60 years.
    - Presence of two or more hemangioblastomas of the retina or brain or a single hemangioblastoma in association with a visceral manifestation such as kidney or pancreatic cysts; renal cell carcinoma; adrenal or extra-adrenal pheochromocytomas; endolymphatic sac tumors; papillary cystadenomas of the epididymis or broad ligament; or neuroendocrine tumors of the pancreas.
    - Presence of a known disease-causing germline mutation in the VHL gene.
4. Any female participant of childbearing potential must not be pregnant or breast-feeding, must have a negative pregnancy test at screening and must be willing to undergo pregnancy testing immediately prior to each treatment.
5. Any female participant of childbearing potential and any male participant able to father children must have (or have a partner who has) had a hysterectomy or vasectomy, be completely abstinent from intercourse or must agree to practice two effective methods of contraception throughout the course of the study and for at least two months following the last administration of combination investigational treatment. Acceptable methods of contraception include:
    - hormonal contraception (i.e., birth control pills, injected hormones, dermal patch or vaginal ring),
    - intrauterine device,
    - barrier methods (diaphragm or condom) with spermicide, or
    - surgical sterilization (hysterectomy, tubal ligation or vasectomy).

3.3.2 Exclusion Criteria

1. Participant has a history or evidence of significant cardiac disease (for example, use of cardiac medications aside from agents to control blood pressure, past acute coronary syndrome, past myocardial infarction, past revascularization procedure or arrhythmias requiring past or present treatment).
2. Participant has a history of stroke or transient ischemic attack. *Note: cerebrovascular manifestations and/or complications of central nervous system hemangioblastomas are not exclusionary, in the absence of past stroke or transient ischemic attack.*
3. Participant has used systemic medication with significant anti-VEGF or anti-PDGF activity within 30 days of study entry or expects use of such a medication within 12 months of study entry.
4. Participant is medically unable to comply with study procedures or follow-up in the judgment of the investigator.
5. Participant has a diagnosis of diabetic mellitus (type 1 or type 2). Any one of the following will be considered sufficient evidence that diabetes is present:
    - Current regular use of insulin for the treatment of diabetes,
    - Current regular use of oral anti-hyperglycemia agents for the treatment of diabetes,
    - Hemoglobin A1C of $\geq 6.5\%$, or
    - Documented diabetes by ADA and/or WHO criteria.

3.4 Study Eye Eligibility Criteria

The participant must have at least one eye meeting all inclusion criteria and none of the exclusion criteria listed below.

3.4.1 Inclusion Criteria

1. Participant has at least one RCH secondary to VHL disease in the study eye that fulfills the following criteria:

a. The RCH must exhibit growth potential with consequent threat to vision. Growth potential with consequent threat to vision is defined by AT LEAST ONE of the following:
    i. Associated intra- or sub-retinal exudation or lipid deposition that, in the judgment of the investigator, reflects ongoing vascular incompetence and is not solely reflective of residual changes following previous treatment or solely secondary to coexistent retinal traction.
    ii. Increased size of the tumor compared to a previous time point as assessed by fundus photography or fluorescein angiography (FA).
    iii. Associated intra-, sub- or pre-retinal hemorrhage not secondary to previous treatment, as assessed by fundus photography or FA.
    iv. The presence of dilated and/or tortuous feeder vessels.
    v. Vitreous cell or haze indicative of vitreous exudation, in the absence of other ocular features potentially responsible for such findings.
b. The RCH, in the judgment of the investigator, is NOT readily treatable using thermal laser because of its size, posterior location, poor previous response to conventional therapy, association with significant exudation, epiretinal proliferation, associated vascular abnormalities such as vascular proliferation or diffusely incompetent retinal vessels, or other factors predictive of a poor response to standard of care approaches.

2. The study eye must have clarity of ocular media and degree of pupil dilation sufficient to permit adequate fundus photography.

3.4.2 Exclusion Criteria

1. The study eye has present or chronic ocular or periocular infection (including any history of ocular herpes zoster).
2. The study eye has chronic glaucoma; OR has received anti-glaucoma medication at any time within 90 days of study entry; OR has significant ocular hypertension, defined as documented intraocular pressure of ≥ 28 mmHg on any occasion in the absence of self-limited acute glaucoma, OR ≥ 24 mmHg on at least two occasions in the absence of self-limited acute glaucoma. *Note: History of self-limited acute glaucoma in a study*

eye, if now resolved and not expected to recur, is not exclusionary. History of glaucoma or ocular hypertension in the fellow eye, if not felt to significantly impact risk of glaucoma in the study eye, is not exclusionary.

3. The study eye has undergone any surgical procedure within 60 days prior to study entry (inclusive of cryotherapy or thermal laser).
4. The study eye has a history of intravitreal injection of an anti-VEGF agent (such as bevacizumab, ranibizumab or aflibercept) within 42 days prior to study entry.
5. The study eye has a history of intravitreal or periocular injection of long-acting corticosteroids (such as triamcinolone acetonide) within 90 days of study entry or history of any sustained-release ocular drug delivery device with reasonable expectation of residual activity in the study eye.

3.4.3 Choice of Study Eye in Cases of Bilateral Eligibility

If both eyes of a participant meet the eligibility criteria, the investigator will choose to enroll one eye in consultation with the participant.

3.5 Outcome Measures

3.5.1 Primary Study Outcome

The primary outcome for the study is the safety of the combination investigational treatment, assessed by tabulation of adverse events (AEs) reported through Week 52.

3.5.2 Secondary Study Outcomes

Secondary outcomes include tabulation of AEs reported through Week 104 and the following measures in the study eye at Weeks 52 and 104:

- the proportion of participants experiencing reduction in size of at least one RCH in the absence of other ablative treatment (assessed by fundus photography and FA);
- the proportion of participants experiencing moderate vision loss (defined as a loss of $\geq$ 15 letters from baseline on electronic visual acuity [EVA] testing);
- mean change in visual acuity;
- change in size of RCH (measured by fundus photography and FA);

- change in exudation (measured by fundus photography, Optical Coherence Tomography [OCT] and FA);
- change in epiretinal proliferation, fibrosis or retinal traction (assessed by OCT and fundus photography);
- the proportion of participants undergoing ablative treatment of RCH or ocular surgery;
- the proportion of participants with successful ablative treatment of RCH; and
- the proportion of participants with appearance of one or more new RCH.

4.0 STATISTICAL CONSIDERATIONS

Since this is a proof-of-principle study, all analyses will be exploratory in nature.

4.1 Sample Size

The accrual goal is three participants. This is an appropriate sample size for the study objectives, since this preliminary investigation will not attempt to definitively determine the safety or efficacy of this treatment.

4.2 Analysis Population

All enrolled participants who received at least one study treatment injection, regardless of whether they discontinued treatment prior to Week 52, will be included in the analysis population. All summaries and listings will be based on the primary analysis population.

4.3 Descriptive Statistics

For continuous parameters, descriptive statistics will include number of observations, mean, standard deviation, median, minimum and maximum. For categorical parameters, frequency and percentage of participants will be summarized; percentages will be based on the number of participants in the primary analysis population.

4.4 Handling of Missing Values

In general, missing observations will be excluded from analyses.

4.5 Adjustment for Multiplicity

Since all analyses are exploratory in nature, no adjustments will be made for multiplicity in any statistical analyses performed.

4.6 Software for Analyses

Statistical analyses will be performed using SAS version 9.4 or higher or R v3.3.1 or higher. All tables, listings and figures presented in the analysis will be created using either SAS v9.4 or Rv3.3.1 or higher.

5.0 DATA SUMMARIES

5.1 Accrual and Participant Characteristics

Demographic data collected include baseline age, sex, race and ethnicity. Demographic data will be listed by participant and will include study registration date and information on study eye.

5.2 Medical and Ophthalmic History

A listing of history of medical and ophthalmic conditions as well as any physical examination findings at baseline will be provided.

5.3 Analysis of Protocol Compliance

Listings of participant-specific and non-participant-specific protocol deviations and unanticipated problems will be presented.

Study Procedure Deviations

This table will present the number of procedures not completed, the expected number of procedures completed, and the percentage of procedures missed for each individual participant and collectively for all participants, cumulatively throughout the study (Table 1). Number of procedures not completed is defined when the site reports a missed procedure or when the protcol monitors note missed procedures at a site, and will be presented as a sum. Expected number of procedures completed is defined based on the study flowsheet included in the protocol, and will also be presented as a sum. Percentage of procedures missed will be calculated as follows:

$$(N_{\text{procedures not completed}} / N_{\text{expected procedures completed}})*100$$

The table will flag occurrences where collectively or individually, participants missed more than 15% of the expected procedures if the number of expected procedures is > 16. Otherwise, if the number of expected procedures is 16 or less, the table will flag occurrences where collectively or individually, participants missed two or more procedures.

Visit Schedule Deviations

This table will present the number of expected visits, number of missed study visits, the percentage of missed study visits, the number of out of window visits, and the percentage of out of window visits for each individual participant and collectively for all participants, cumulatively throughout the study (Table 2). Number of expected, missed and out of window study visits will be calculated from the study flowsheet and will all be presented as sums. The percentage of missed study visits will be calculated as:

$$(N_{\text{visits missed}} / N_{\text{expected visits}}) * 100$$

Similarily, the percentage of out of window study visits will be calculated as:

$$(N_{\text{visits out of window}} / N_{\text{expected visits}}) * 100$$

If the number of expected visits is > 16, then the table will flag occurrences where collectively or individually participants missed more than 15% of the expected visits; similarly, the table will flag occurrences where collectively or individually participants completed more than 15% of the expected visits outside of the window.

Otherwise, if the number of expected visits is 16 or less, then the table will flag occurrences where collectively or individually participants mised or completed out of window two or more visits.

6.0 TREATMENT

Information related to injections administered at each visit will be listed.

7.0 PRIMARY OUTCOMES ANALYSIS

The analysis of primary outcome will be considered exploratory; no formal statistical analysis will be performed.

All treatment-emergent ocular and systemic AEs reported through Week 52 will be summarized. Treatment-emergent AEs are those events occurring at the time of or after administration of first

dose of study drug. Frequency and percentage of particpants, total number of AEs and number of AEs experienced by each participant will be summarized by seriousness, severity of the AE, relatedness to the study treatment and Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC); tabulations will also be provided by timing of occurrence of AEs (while on treatment vs. after discontinuaion of treatment) (Tables 3 and 4).

8.0 SECONDARY OUTCOMES ANALYSIS

The analysis of secondary outcomes will be considered exploratory. Therefore, no formal statistical analysis will be performed. In addition to the data summaries detailed below, exploratory plots showing values over time for relevant measurements may be presented.

8.1 Adverse Events (AEs)

All ocular and systemic AEs reported through Week 104 will be tabulated similar to the primary outcome (Tables 5 and 6).

8.2 Retinal Capillary Hemangioma(s) (RCH)

The following will be assessed as secondary outcomes at Weeks 52 and 104 compared to baseline; information will also be presented for each participant separately (Table 7).

- Frequency and percentage of participants with reduction in size of at least one RCH, in the absence of other ablative treatment assessed by fundus photography and FA;
- Frequency and percentage of participants with increase, decrease, mixed effects and no change in size of RCH measured by fundus photography and FA;
- Frequency and percentage of participants with increase, decrease, mixed effects and no change in exudation measured by fundus photography, OCT and FA;
- Frequency and percentage of participants with increase, decrease, mixed effects and no change in epiretinal proliferation, fibrosis or retinal traction assessed by OCT and fundus photography;
- Frequency and percentage of participants undergoing ablative treatment of RCH or ocular surgery;
- Frequency and percentage of participants with successful ablative treatment of RCH;
- Frequency and percentage of participants with appearance of one or more new RCH.

8.3 Electronic Visual Acuity (EVA)

Binocular visual acuity measures and visual acuity measures for each eye will be obtained using an EVA algorithm. EVA with manifest refraction will be performed if a change in EVA ≥ 10 E-ETDRS letters (≥ 0.20 logMAR) since previous visit is observed.

Summary statistics for change in total letters read at Weeks 52 and 104 compared to baseline will be presented. Frequency and percentage of participants with moderate vision loss at Weeks 52 and 104, defined as loss of ≥ 15 letters from baseline, will also be summarized (Table 8). Values from assessments performed with manifest refraction will be used for the analysis if available; otherwise, values from assessments performed without manifest refraction will be used.

9.0 SAFETY ANALYSIS

In addition to the data summaries detailed below, exploratory plots showing values over time for relevant measurements may be presented.

9.1 Natural Progressions of the Disease

All natural progressions of the disease reported through Week 104 will be listed.

9.2 Post-Injection Evaluation

Intraocular pressure (IOP) in the injected eye is measured by Tono-Pen within 20 minutes after injection. Post-injection IOP and change from pre-injection measurement will be summarized for each visit (Table 10). Frequency and percentage of participants with the following will be presented for each visit:

- > 24 mmHg IOP after injection in the treated eye (Table 10);
- Severe pain, absence of hand-motion vision or absence of perfusion of the retinal arterioles following an injection (Table 9);
- Intraocular inflammation as assessed by the presence of anterior chamber or vitreous cell on ophthalmoscopy by grade (Table 9); and
- Any other complications following an injection (Table 9).

9.3 Intraocular Pressure (IOP)

Summary statistics of baseline and change from baseline in IOP at each visit will be presented (Table 10). If study treatment is administered at a visit, then the pre-injection value will be used in the summaries. Post-injection values are summarized as described in Section 9.2.

9.4 EVA

Summary statistics of baseline and change from baseline in total letters read at each visit will be presented (Table 11).

9.5 Other Ophthalmologic Assessments

All ophthalmologic data collected will be descriptively summarized. If appropriate, exploratory plots may be presented.

If sufficient data are available, frequency and percentage of participants who meet the definition of clinical improvement and time to clinical improvement will also be summarized; otherwise, the data will be listed.

9.6 Laboratory Assessments

Laboratory testing includes a complete blood count (CBC), hemoglobin A1C and acute care, hepatic and mineral panels, and may be completed within one month (31 days) of the baseline visit. Laboratory testing excluding hemoglobin A1C will also occur at Weeks 16 and 104.

A listing of all laboratory assessments and any abnormalities noted will be presented.

9.7 Treatment Discontinuation and Participant Withdrawal

Participants who discontinue treatment early or withdraw from the study, including timing and reason for treatment discontinuation or withdrawal, will be listed.

10.0 QUALITY ASSURANCE PLANS

To ensure accurate, reliable study results, two statisticians will separately analyze and compare the study outcomes. All SAS or R code use to generate primary and secondary outcomes will undergo a code validation by an independent statistician or SAS programmer.

Documentation related to code validation audits will be maintained on file at the Coordinating Center.

11.0 REFERENCES

1. Schimke RN, Collins DL, Stolle CA. Von Hippel-Lindau Syndrome. In: Pagon RA, Bird TD, Dolan CR, eds. Gene Reviews. 2010/03/20 ed. Seattle: University of Washington; 1993.
2. Melmon KL, Rosen SW. Lindau's disease. Review of the literature and study of a large kindred. Am J Med 1964;36:595-617.

12.0 MOCK SHELLS

12.1 Protocol Compliance

Table 1: Missed Study Procedures

Participant Number	Number of Procedures Not Completed[1]	Expected Number of Procedures Completed[2]	Percentage of Procedures Missed (%)
xxx	xx	xx	x.x
xxx	xx	xx	x.x
xxx	xx	xx	x.x
Total	xx	xx	x.x

[1]Procedures not completed are defined when the site reports a missed procedure or when the protocol monitors note missed procedures at a site visit.
[2]Expected number of procedures is defined based on the study flowsheet included in the protocol.
Highlighted cells indicate percentage of missed procedures above the protocol-defined threshold of 15%.

Table 2: Missed and Out of Window Study Visits

Participant Number	Number of Missed Study Visits	Number of Out of Window Study Visits	Expected Number of Follow-up Visits	Percentage of Visits Missed[1]	Percentage of Visits Out of Window[1]	Study Visits Missed or Out of Window
xxx	xx	xx	xx	x.x	x.x	xxx
xxx	xx	xx	xx	x.x	x.x	xxx
xxx	xx	xx	xx	x.x	x.x	xxx
Total	xx	xx	xx	x.x	x.x	xxx

[1]The numbers in these cells reference the percentage of missed or out of window visits for all study participants because the protocol references the overall study visits threshold at 15% of missed or out of window study visits.
Highlighted cells indicate percentage of missed or out of window visits above the protocol-defined threshold of 15%.

12.2 Primary Outcome Analysis

Table 3: Summary of Adverse Events through Week 52

	Number of Events N			While on Treatment		After Discontinuation of Treatment		Total	
	Participant ID			Participants with Events N (%)[1]	Number of Events N	Participants with Events N (%)[1]	Number of Events N	Participants with Events N (%)[1]	Number of Events N
	XXX	XXX	XXX						
All AEs	x	x	x	x (x%)	x	x (x%)	x	x (x%)	x
Serious Adverse Events	x	x	x	x (x%)	x	x (x%)	x	x (x%)	x
Severity	x	x	x	x (x%)	x	x (x%)	x	x (x%)	x
Mild	x	x	x	x (x%)	x	x (x%)	x	x (x%)	x
Moderate	x	x	x	x (x%)	x	x (x%)	x	x (x%)	x
Severe	x	x	x	x (x%)	x	x (x%)	x	x (x%)	x
Life-threatening	x	x	x	x (x%)	x	x (x%)	x	x (x%)	x
Death	x	x	x	x (x%)	x	x (x%)	x	x (x%)	x
Ocular Specification	x	x	x	x (x%)	x	x (x%)	x	x (x%)	x
Non-ocular	x	x	x	x (x%)	x	x (x%)	x	x (x%)	x
Study Eye	x	x	x	x (x%)	x	x (x%)	x	x (x%)	x
Non-Study Eye	x	x	x	x (x%)	x	x (x%)	x	x (x%)	x
Relation to Treatment	x	x	x	x (x%)	x	x (x%)	x	x (x%)	x
Related	x	x	x	x (x%)	x	x (x%)	x	x (x%)	x
Not Related	x	x	x	x (x%)	x	x (x%)	x	x (x%)	x

[1]Denominators are the number of participants in the primary analysis population.

Table 4: Adverse Events through Week 52 by MedDRA System Organ Class

	Number of Events N			While on Treatment		After Discontinuation of Treatment		Total	
	Participant ID			Participants with Events N (%)[1]	Number of Events N	Participants with Events N (%)[1]	Number of Events N	Participants with Events N (%)[1]	Number of Events N
	XXX	XXX	XXX						
System Organ Class 1	x	x	x	x (x%)	x	x (x%)	x	x (x%)	x
System Organ Class 2	x	x	x	x (x%)	x	x (x%)	x	x (x%)	x
System Organ Class 3	x	x	x	x (x%)	x	x (x%)	x	x (x%)	x
...	x	x	x	x (x%)	x	x (x%)	x	x (x%)	x
...	x	x	x	x (x%)	x	x (x%)	x	x (x%)	x

[1]Denominators are the number of participants in the primary analysis population.

12.3 Secondary Outcome Analysis

Table 5: Summary of Adverse Events through Week 104

This table will be similar to Table 3.

Table 6: Adverse Events through Week 104 by MedDRA System Organ Class

This table will be similar to Table 4.

Table 7: Analysis of Secondary Outcomes Relating to RCH

	Week 52				Week 104			
	Participant ID			Total	Participant ID			Total
	XXX	XXX	XXX	N (%)[1]	XXX	XXX	XXX	N (%)[1]
Reduction in Size of at least One RCH in the Absence of Other Ablative Treatment	Yes/No	Yes/No	Yes/No	x (x%)	Yes/No	Yes/No	Yes/No	x (x%)
Change in Size of RCH from Baseline	xxx	xxx	xxx		xxx	xxx	xxx	
Increase				x (x%)				x (x%)
Decrease				x (x%)				x (x%)
Mixed Effects				x (x%)				x (x%)
No Change				x (x%)				x (x%)
Change in Exudation from Baseline	xxx	xxx	xxx		xxx	xxx	xxx	
Increase				x (x%)				x (x%)
Decrease				x (x%)				x (x%)
Mixed Effects				x (x%)				x (x%)
No Change				x (x%)				x (x%)
Change in Epiretinal Proliferation/ Fibrosis/Retinal Traction from Baseline	xxx	xxx	xxx		xxx	xxx	xxx	
Increase				x (x%)				x (x%)
Decrease				x (x%)				x (x%)
Mixed Effects				x (x%)				
No Change				x (x%)				x (x%)

Table 7: Analysis of Secondary Outcomes Relating to RCH (Continued)

	Week 52				Week 104			
	Participant ID			Total	Participant ID			Total
	XXX	XXX	XXX	N (%)[1]	XXX	XXX	XXX	N (%)[1]
Undergoing Ablative Treatment of RCH or Ocular Surgery	Yes/No	Yes/No	Yes/No	x (x%)	Yes/No	Yes/No	Yes/No	x (x%)
Successful Ablative Treatment of RCH	Yes/No	Yes/No	Yes/No	x (x%)	Yes/No	Yes/No	Yes/No	x (x%)
Appearance of One or More New RCH	Yes/No	Yes/No	Yes/No	x (x%)	Yes/No	Yes/No	Yes/No	x (x%)

[1]Percentages are based on the number of participants in the primary analysis population.

Table 8: Analysis of Secondary Outcome of EVA

		Change from Baseline	
	Baseline	**Week 52**	**Week 104**
EVA Total Letters Read			
N	x	x	x
Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)
Median	x	x	x
Range (Min, Max)	x, x	x, x	x, x
Participants with Moderate Vision Loss (Loss of ≥ 15 Letters Read from Baseline), N (%)[1]		x (x%)	x (x%)

[1]Denominators are the number of participants in the primary analysis population.

12.4 Safety Analysis

Table 9: Summary of Post-Injection Evaluations

	Anterior Chamber Cells N (%)[1] Grade				Vitreous Cells N (%)[1] Grade				Severe Pain, Absence of Hand Motion Vision or Absence of Perfusion of the Retinal Arterioles N (%)[1]	Any Other Post-Injection Complications N (%)[1]
	0, 0.5 or T	1-2	3	4	0, T	1-2	3	4		
At least Once During the Study										
Study Eye	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Non-Study Eye	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)		
Baseline										
Study Eye	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Non-Study Eye	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)		
Week 4										
Study Eye	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Non-Study Eye	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)		
…										
…										
Week XX										
Study Eye	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Non-Study Eye	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)		
Week 104										
Study Eye	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)		
Non-Study Eye	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)		

[1]Denominators are the number of participants in the primary analysis population.

Table 10: Summary of IOP Over Time

	Pre-Injection IOP Measurements (mmHg)				Post-Injection IOP Measurements (mmHg)	
	Pre-Injection IOP		Change from Baseline in Pre-Injection Measurements		Study Eye	
	Study Eye	Non-Study Eye	Study Eye	Non-Study Eye	Post-Injection IOP	Change from Pre-Injection Measurement
Baseline						
N	x	x			x	x
Mean (SD)	x.x (x.x)	x.x (x.x)			x.x (x.x)	x.x (x.x)
Median	x.x	x.x			x.x	x.x
Range (Min, Max)	x.x, x.x	x.x, x.x			x.x, x.x	x.x, x.x
IOP > 24 mmHg, N (%)[1]					x (x%)	
Week 4						
N	x	x	x	x	x	x
Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
Median	x.x	x.x	x.x	x.x	x.x	x.x
Range (Min, Max)	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
IOP > 24 mmHg, N (%)[1]					x (x%)	
Week 8						
N	x	x	x	x	x	x
Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
Median	x.x	x.x	x.x	x.x	x.x	x.x
Range (Min, Max)	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
IOP > 24 mmHg, N (%)[1]					x (x%)	
...						
...						
Week XX						
N	x	x	x	x	x	x
Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
Median	x.x	x.x	x.x	x.x	x.x	x.x
Range (Min, Max)	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
IOP > 24 mmHg, N (%)[1]					x (x%)	

Table 10: Summary of IOP Over Time (Continued)

	Pre-Injection IOP Measurements (mmHg)				Post-Injection IOP Measurements (mmHg)	
	Pre-Injection IOP		Change from Baseline in Pre-Injection Measurements		Study Eye	
	Study Eye	Non-Study Eye	Study Eye	Non-Study Eye	Post-Injection IOP	Change from Pre-Injection Measurement
Week 104						
N	x	x	x	x		
Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)		
Median	x.x	x.x	x.x	x.x		
Range (Min, Max)	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x		

[1]Denominators are the number of participants in the primary analysis population.

Table 11: Summary of EVA Total Letters Read Over Time

	EVA Total Letters Read		Change from Baseline	
	Study Eye	Non-Study Eye	Study Eye	Non-Study Eye
Baseline				
N	x	x		
Mean (SD)	x.x (x.x)	x.x (x.x)		
Median	x.x	x.x		
Range (Min, Max)	x.x, x.x	x.x, x.x		
Week 4				
N	x	x	x	x
Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
Median	x.x	x.x	x.x	x.x
Range (Min, Max)	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
Loss of ≥ 15 Letters, N (%)[1]			x (x%)	x (x%)
...				
...				
Week XX				
N	x	x	x	x
Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
Median	x.x	x.x	x.x	x.x
Range (Min, Max)	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
Loss of ≥ 15 Letters, N (%)[1]			x (x%)	x (x%)
...				
...				
Week 104				
N	x	x	x	x
Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
Median	x.x	x.x	x.x	x.x
Range (Min, Max)	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
Loss of ≥ 15 Letters, N (%)[1]			x (x%)	x (x%)

12.5 Listings

Listings will be by participant (except for non-participant specific protocol deviations and unanticipated problems) and will include all relevant raw data points captured and any relevant derived values.