Statistical Analysis Plan

For

A Pilot Study for the Evaluation of Minocycline as a Microglia Inhibitor in the Treatment of Central Retinal Vein Occlusions

Version 1.0

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Prepared by Megan Wall

Original Author Signature: _____

Megan Wall, MS

Reviewer Signature: _____

Michael Rothe, MS

Principal Investigator Signature: _____

Catherine Cukras, MD, PhD

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1.0 INTRODUCTION

This statistical analysis plan (SAP) provides the proposed analyses for the MiCRVO protocol titled "A Pilot Study for the Evaluation of Minocycline as a Microglia Inhibitor in the Treatment of Central Retinal Vein Occlusions". This document contains fifteen sections: (1) background of the study, (2) data sources for analyses, (3) an overview of the study design, (4) statistical considerations, (5) participant disposition, (6) participant characteristics, (7) participant compliance, (8) treatment, (9) criteria for stopping the study, (10) statistical analysis for the primary outcome, (11) statistical analyses for the secondary outcomes, (12) review of safety analyses, (13) quality assurance plans, (14) references, and (15) proposed data tables, figures and listings. This document is based on version 22.0 of the protocol dated December 10, 2019.

1.1 Central Retinal Vein Occlusions (CRVO)

Retinal vein occlusions (RVOs) are a significant source of vision loss, affecting mostly healthy people over 55 years of age. The common source of vision loss is the macular edema accompanying the retinal injury. The two main types of RVOs are branch retinal vein occlusions (BRVO) and central retinal vein occlusions (CRVO). Prevalence of CRVO is approximately 0.1% (1, 2). The fundamental cause of macular edema associated with RVOs is not completely understood, but it is increasingly clear that its pathophysiology extends beyond microvascular disease to involve immune mediators in the retina, such as microglia. Retinal microglia, derived from the monocytic lineage, are resident cells in the healthy retina that may be construed as representatives of the immune system in the immune-privileged environment of the retina. There is accumulating evidence that retinal microglia are associated with inflammation in the retina in conditions such as diabetic retinopathy and the RVOs. Therefore, microglia represent a promising cellular target for forms of therapy that limit the deleterious inflammatory changes found in vein occlusions. Minocycline, a second-generation tetracycline with anti-inflammatory properties and high lipophilicity, appears to inhibit the activation of microglia as has been observed in animal studies and culture (3-6). Minocycline is used widely clinically and has been shown to be well tolerated when used at the FDA-approved doses proposed in this study. The objective of this study is to investigate the safety and potential efficacy of minocycline, a microglia inhibitor, in the treatment of CRVO.

2.0 DATA SOURCE

Data received from the National Eye Institute (NEI) will be collected via their electronic data capture system (EMR), and uploaded on a daily basis to the Coordinating Center's database, Advantage EDC. Microperimetry data will be provided directly to the Coordinating Center from the NEI. Data received from the Bristol Eye Hospital (BEH) will be collected directly through Advantage EDC.

3.0 GENERAL REVIEW OF STUDY DESIGN

3.1 Randomization, Masking and Unmasking

After the participant is determined eligible and has completed the informed consent process, the group will be assigned based on a predetermined randomization schedule developed by the Coordinating Center. Randomization will be stratified by site.

Randomization must occur on the same day as the initial administration of investigational product (IP) while the participant and the ophthalmologist are present and will not be permitted any time before. Participant eligibility must be confirmed before a participant is randomized. Participants will be randomized to one of two groups with equal probability for equal numbers of participants in each group: minocycline or placebo. Participants must continue to receive the same treatment regimen to which they were assigned for the duration of the study.

All clinic staff and participants will be masked to group assignments. Only designated pharmacy personnel, select individuals at the Emmes Company, LLC, and the NEI Data and Safety Monitoring Committee (DSMC) will have access to the group assignments.

Participants will be unmasked if deemed clinically necessary by the examining physician and if the study Principal Investigator (PI) and DSMC Chair are in agreement. In the case of a medical emergency, the examining or treating physician will have the final decision and unilateral right for unmasking. A request for unmasking, after approval by the PI and the DSMC Chair, will be made to Coordinating Center personnel, who will inform the PI and the DSMC Chair of the group assignment. Attempts should be made to maintain the masking of the investigators prior to the study-wide unmasking. Unmasking will be recorded on an adverse event (AE) form. All instances of unmasking must be reported to the ICRRC, the NIH IRB, and the DSMC. At the conclusion of the study, all investigators will be unmasked.

3.2 Study Design

For the NEI Site: The study duration will be 24 months. During this period, participants will be instructed to take the IP (either placebo or minocycline 100 mg capsule) twice daily. The primary outcome will be assessed at Month 12, and secondary outcomes will be assessed at 3, 6, 12, 18 and 24 months. Visits will occur at baseline, and then monthly or as clinically indicated. The study will require a minimum of 25 visits (baseline and Months 1-24). All appointments must be conducted within a window of ± seven days from the target day. The tests scheduled at each visit will be completed in one day. At each visit, the participant will undergo a review of systems and an assessment of safety variables. A complete ophthalmologic examination will be performed at each visit to measure outcome variables.

During each clinic visit, participants will have their visual acuity measured and will undergo OCT testing to measure retinal thickness.

For the BRC Sites: The study duration will be approximately 24 months. During this period, participants will be instructed to take the IP (either placebo or minocycline 100 mg capsule) twice daily. The primary outcome will be assessed at Month 12, and secondary outcomes will be assessed at 3, 6, 12, 18 and 24 months. Visits will occur at baseline, and then monthly or as clinically indicated. The study will require a minimum of 26 appointments (baseline and Months 1-24 and safety follow-up). All appointments must be conducted within a window of ± seven days from the target day, except for the safety follow-up visit which must occur at least five days after the cessation of IP. The tests scheduled at each visit are expected to be completed in one day, with the exception of the baseline visit, Month 12 visit and Month 24 visit. If the baseline examinations cannot be performed in one clinic visit over one day, it is acceptable that the baseline examinations be completed at subsequent clinic visits, if scheduled within fourteen days of the first visit. If the Month 12 and Month 24 examinations cannot be performed in one clinic visit over one day, it is acceptable that the examinations be completed at subsequent clinic visits, if scheduled within seven days of the first visit. At each visit, the participant will undergo a review of systems and an assessment of safety variables. A complete ophthalmologic examination will be performed at each visit (except for the safety follow-up visit) to measure outcome variables. If the baseline visit, Month 12 visit, or Month 24 visit are conducted over more than one day, BCVA, OCT and microperimetry testing must be conducted on the day of the injection. If a participant or site is

unable to complete microperimetry testing, the testing may be waived and the investigator will specify the reason the test could not be completed.

During each study visit, with the exception of the Month 24 visit and safety follow-up visit at the BRC sites, IP will be dispensed to the participant unless the treatment is deemed to be "worsening" or to offer "no improvement" and the participant and the investigator decide to stop IP. An information sheet outlining instructions on taking the study medication and concomitant mediations will be distributed to participants and discussed in detail by study personnel. They will be asked to inform any physician who is prescribing new medications that they are currently taking minocycline. In addition, the participants will be asked to inform a study team member if a new medication is prescribed to them.

Participant compliance with IP will be prompted through ongoing encouragements and reminders during study visits and scheduled and unscheduled telephone contacts. Compliance will be assessed by pill counts conducted during study visits and the participant's pill diary.

Once identified, occurrences in which the computed compliance rate between study visits falls below 50% will be reported as a protocol deviation to the NIH IRB within two weeks using iRIS.

3.2.1 Treatment Prior to Month 3

At baseline, the participant will receive an injection of 1.25 mg bevacizumab, an anti-VEGF agent, and also start the randomized IP. At Months 1 and 2, the participant will again receive bevacizumab injections in the study eye and continue the randomized IP.

3.2.2 Treatment Beginning at Month 3

Visual acuity and macular edema will be evaluated at study visits to determine further treatment. Starting at Month 3 and at every visit thereafter, the following scenarios will be considered. The participant will be re-injected with bevacizumab unless the participant meets the "improvement," "worsening," "new steady state" or "no improvement" criteria defined below.

Scenario 1: If the participant meets the "improvement" criteria, the participant will continue to take the IP, but the bevacizumab injection will be withheld at that visit.

Scenario 2: If the participant meets the "worsening" criteria, the participant will be offered any therapy available at the discretion of the treating investigator, including:

a. Anti-VEGF Treatment.

b. Intravitreal or Periocular Steroid Injections.

Scenario 3: If the participant does not meet the "improvement" or "worsening" criteria, but meets the "new steady state" criteria, the treating investigator physician will have the discretion to hold bevacizumab injections until the OCT changes (worsens) by > 25 microns from this "new steady state" level.

At the Month 12 visit and at every visit thereafter, Scenarios 1, 2 and 3 will be considered as well as the following scenario, which allows for a study physician to determine whether there has been "no improvement" in the participant's condition:

Scenario 4: If the participant meets the "no improvement" criteria or if the investigator's clinical impression is that there has been no improvement in the study eye, the participant will be offered therapy at the discretion of the treating investigator. The decision to re-inject the participant with bevacizumab (the anti-VEGF agent) will be made by the treating investigator after consulting with the participant. The decision to continue the IP will also be made by the treating investigator after consulting with the participant.

The "improvement," "worsening," "new steady state," and "no improvement" criteria are defined as follows:

- *Improvement*: Visual acuity in the study eye of ≥ 84-88 letters (20/20) OR OCT central subfield thickness < 300 microns.
- *Worsening*: A decrease in visual acuity of ≥ 15 or more letters in the study eye compared to baseline, AND an increase in OCT subfield thickness ≥ 1-step log unit compared to baseline for at least two consecutive visits.
- *New steady state*: Improvement and worsening criteria not met and central subfield thickness remains ≥ 300 microns on OCT, but thickness is stable and has not changed > 25 microns over the last three consecutive injections.
- *No improvement*: Improvement and worsening criteria are not met and visual acuity failed to increase by ≥ 10 letters in the study eye compared to baseline AND OCT central subfield thickness failed to decrease by ≥ 1-step log unit compared to baseline.

3.2.3 Criteria for Stopping the Study

The DSMC may recommend temporarily suspending or closing enrollment, or stopping the study at any time due to safety concerns, demonstration of efficacy or lack of efficacy, or slow recruitment. Criteria for stopping the study include the following:

- A sufficiently large number of dropouts occurs as to make the trial likely to be uninformative;
- A participant experiences a drop in BCVA in the study eye of ≥ 30 letters from baseline attributed to the IP;
- A participant experiences a serious adverse event (SAE), drug reaction or complication, whether attributed to the IP or not, which has an impact on visual function or any other body system or precludes continuation of the IP. This would include the development of hypersensitization, allergic responses or other potentially serious drug reactions to medications required by the protocol.

Following premature IP discontinuation, not due to an AE, participants will continue to be followed as per the protocol.

3.3 Study Objective

The objective of this study is to investigate the safety and potential efficacy of minocycline, a microglia inhibitor, in the treatment of CRVO.

3.4 Study Population

A minimum of 10 and a maximum of 20 participants who meet the eligibility criteria may be enrolled.

3.4.1 Inclusion Criteria

To be eligible, the following inclusion criteria must be met, where applicable.

1. Participant is 18 years of age or older.
2. Participant must understand and sign the protocol's informed consent document.

3. Female participants of childbearing potential must not be pregnant or breast-feeding and must be willing to undergo serum (BRC sites only) and urine pregnancy tests throughout the study.

4. For the NEI Site: Female participants of childbearing potential and male participants 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 acceptable methods of contraception throughout the course of the study and for one week after study medication discontinuation (based on the half life of minocycline which is 11-22 hours). Acceptable methods of contraception include:

    - hormonal contraception (i.e., birth control pills*, injected hormones, dermal patch or vaginal ring),
    - intrauterine device,
    - barrier methods (diaphragm, condom) with spermicide, or
    - surgical sterilization (hysterectomy or tubal ligation).

    *Oral birth control pills must be used with caution as minocycline decreases the effectiveness of some oral contraceptives. Participants already taking oral contraceptives may continue to use them, but must agree to use at least one other method of birth control while on study.

5. For the BRC Sites: Female participants of childbearing potential and male participants able to father children must have (or have a partner who has) had a hysterectomy or vasectomy, or be completely abstinent from intercourse. Male participants or male partners (of female participants) who have not had a vasectomy or are not abstinent are required to use a condom with spermicide throughout the course of the study and for one week after study medication discontinuation (based on the half life of minocycline which is 11-22 hours). Female participants of childbearing potential or female partners (of male participants) of childbearing potential must practice one of the below acceptable methods of contraception throughout the course of the study and for one week after study medication discontinuation:

    - hormonal contraception (i.e., birth control pills*, injected hormones, dermal patch or vaginal ring),

- intrauterine device,
- barrier methods (diaphragm, condom) with spermicide, or
- surgical sterilization (hysterectomy or tubal ligation).

Abstinence is only acceptable when it is the participant's preferred and usual lifestyle choice. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

*Oral birth control pills must be used with caution as minocycline decreases the effectiveness of some oral contraceptives. Participants already taking oral contraceptives may continue to use them, but must agree to use at least one other method of birth control while on study.

It should be noted that two forms of contraception (as specified above) will be used by sexually active participants for the duration of the study and for one week after study medication discontinuation.

6. Participants must agree to notify the study investigator or coordinator if any of their doctors initiate a new medication during the course of the study.
7. Participant must have normal renal function and liver function or have mild abnormalities not above grade 1 as defined by the Common Terminology Criteria for Adverse Events v4.0 (CTCAE).
8. Participant has at least one eye that meets the study eye criteria listed in Section 3.5.

3.4.2 Exclusion Criteria

A participant is not eligible if any of the following exclusion criteria are present.

1. Participant is in another investigational study and actively receiving IP for CRVOs.
2. Participant is unable to comply with study procedures or follow-up visits.
3. Participant has a known hypersensitivity to sodium fluorescein dye.
4. Participant has a condition that, in the opinion of the investigator, would preclude participation in the study (e.g., unstable medical status including blood pressure and glycemic control).

5. Participant has a history of chronic renal failure requiring dialysis or kidney transplant.
6. Participant has a history of chronic hepatitis or liver failure.
7. Participant has an allergy or hypersensitivity to minocycline or any drug in the tetracycline family.
8. Participant is currently taking a tetracycline medication.
9. Participant is taking any medication that could adversely interact with minocycline such as methoxyflurane.
10. Participant has a blood pressure of > 180/110 (systolic above 180 **OR** diastolic above 110).
    - If blood pressure is brought below 180/110 by anti-hypertensive treatment, the participant can become eligible.
11. Participant is currently being treated with systemic anti-VEGF agents or systemic steroids.
12. Participant had a cerebral vascular event (CVA) or myocardial infarction (MI) within three months prior to study entry.
13. Participant has a history of thyroid cancer.

3.5 Study Eye Eligibility Criteria

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

3.5.1 Study Eye Inclusion Criteria

1. The study eye has a best-corrected ETDRS visual acuity score between 78 and 34 letters (i.e., between 20/32 and 20/200).
2. The study eye shows definite retinal thickening due to a CRVO based on clinical examination involving the center of the macula that is not refractory to further therapy as based on the investigator's clinical judgment. CRVO is defined as an eye that had retinal hemorrhage or other biomicroscopic evidence of RVO (e.g., telangiectatic capillary bed) and a dilated (or previously dilated) venous system in at least three quadrants of the retina drained by the affected vein.

3. The study eye has retinal thickness in the central subfield on baseline OCT measurement > 350 microns, as measured by Zeiss Cirrus spectral domain OCT, or an equivalent retinal thickness on a similar OCT machine.
4. The study eye has media clarity and pupillary dilation sufficient for adequate fundus photographs. Furthermore, the participant must be able to cooperate during the procedure for accurate fundus photographs.

3.5.2 Study Eye Exclusion Criteria

1. The study eye has macular edema considered to be due to a cause other than CRVO.
2. An eye should not be considered eligible if:
   - The macular edema is considered to be related to cataract extraction, or
   - Clinical examination and/or OCT suggest that vitreoretinal interface disease (e.g., a taut posterior hyaloid or epiretinal membrane) is the primary cause of the macular edema, or
   - Clinical examination, medical history and/or fluorescein angiography suggest that diabetic retinopathy is the primary cause of the edema.
3. The study eye has a history of a recurrent RVO.
4. The study eye has a history of RVO present for > 18 months.
5. A brisk afferent pupillary defect (APD) is present in the study eye.
6. An ocular condition (other than RVO) is present in the study eye such that, in the opinion of the investigator, visual acuity would not improve from resolution of macular edema (e.g., foveal atrophy, pigmentary changes, dense subfoveal hard exudates, laser scar at fovea, non-retinal condition).
7. An ocular condition (other than RVO) is present that, in the opinion of the investigator, might affect macular edema or alter visual acuity during the course of the study (e.g., vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, Irvine-Gass Syndrome, etc.).
8. A substantial cataract that, in the opinion of the investigator, is likely to be decreasing visual acuity by three lines or more (i.e., cataract would be reducing acuity to 20/40 or worse if eye was otherwise normal) is present in the study eye.

9. The study eye has had panretinal or sectoral scatter photocoagulation (PRP) within four months prior to study entry.
10. The study eye has had pars plana vitrectomy within six months prior to study entry.
11. The study eye has undergone major ocular surgery (including cataract extraction, scleral buckle, any intraocular surgery, etc.) within three months prior to study entry.
12. A yttrium aluminum garnet (YAG) capsulotomy has been performed on the study eye within two months prior to study entry.
13. The study eye has had treatment < three months prior to study entry of intravitreal or periocular steroid injections.
14. The study eye has had treatment < 28 days prior to study entry of intravitreal anti-VEGF agents.

3.5.3 Choice of Study Eye in Cases of Bilateral Eligibility

If both eyes of a participant meet the criteria described in Sections 3.5.1 and 3.5.2, the study eye will be determined at the investigator's discretion.

3.6 Outcome Measures

3.6.1 Primary Study Outcome

The primary outcome is the difference in mean change of BCVA, as measured in ETDRS letters, between the minocycline and placebo groups in the study eye at 12 months compared to baseline.

3.6.2 Secondary Study Outcomes

Secondary outcomes include the difference between the minocycline and placebo groups in the:

- Number of bevacizumab injections from baseline to 12 months and from baseline to 24 months,
- Changes in mean macular sensitivity as measured by microperimetry at 3, 6, 12, 18 and 24 months compared to baseline,
- Mean change in the ETDRS BCVA in the study eye at 24 months compared to baseline,
- Changes in the retinal thickness in the study eye as measured by OCT at 6, 12, 18 and 24 months compared to baseline,

- Number of participants improving ≥ 1 logOCT scale step at 12 and 24 months compared to baseline,
- Changes in fluid leakage in the macular as demonstrated by fluorescein angiography at 12 and 24 months compared to baseline.

3.6.3 Safety Outcomes

Safety outcomes will be the number and severity of systemic and ocular toxicities and AEs. The number of participants withdrawn from the IP due to vision loss or AEs and the number of participants deemed to have worsening disease will also contribute to the assessment of safety.

4.0 STATISTICAL CONSIDERATIONS

4.1 Sample Size

No formal sample size has been calculated. The accrual ceiling for this study is 20 participants (10 per group) with a minimum of 10 participants (five per group). This number was selected to obtain at least five participants in each group reaching the final study visit in order to obtain preliminary data to potentially support a larger trial if promising results are revealed.

4.2 Analysis Population

The following analysis populations will be considered for this study:

Enrolled population: Includes all participants enrolled in the study, regardless of compliance, follow-up or treatment received.

Safety population: Includes all participants who were exposed to IP, regardless of adherence to the protocol.

Primary outcome analysis population: Includes those participants who were exposed to IP and were followed up for at least 12 months.

4.3 Descriptive Statistics

For continuous parameters, such as visual acuity, central retinal thickness as measured by optical coherence tomography, and macular sensitivity as measured by microperimetry, descriptive statistics will include the number of observations, mean, standard deviation, median, minimum

and maximum. For categorical parameters, such as changes in fluid leakage as demonstrated by fluorescein angiography, frequency and percentage of participants will be summarized.

4.4 Handling of Missing Values

If IP compliance cannot be determined for a participant due to missing capsule counts, IP compliance will be imputed by taking the median of all available capsule counts recorded at previous study visits.

All other missing observations will be excluded from analyses.

4.5 Handling Duplicate Assessments

If participants completed assessments at both scheduled and supplementary visits, the assessments from the scheduled visit will be considered in the analysis and tabular summaries. However, if an assessment is completed only at supplementary visits, then the assessments from the most recent supplementary visit will be included in the analysis and tabular summaries. Results of all assessments, including those performed during supplementary visits, will be included in the listings.

4.6 Software for Analyses

Statistical analyses will be performed using SAS version 9.4 or higher or R v3.6.1 or higher. All tables, listings and figures presented in the analysis will be created using either SAS v9.4 or Rv3.6.1 or higher.

5.0 PARTICIPANT DISPOSITION

Overall participant disposition including the number and percentage of participants enrolled, completed 12 months of treatment, completed the study and discontinued the study early will be summarized. Reasons for study discontinuation will also be summarized (Table 1). The number and percentage of participants who withdraw from IP due to safety, including due to vision loss (manually identified based on investigator's comments for those participants with reason for withdrawal from IP indicated as "safety withdrawal") and AEs (reason for withdrawal from IP indicated as "safety withdrawal" for the occurrence of AEs assessed as being related to study IP that preclude further administration of IP) will be included. Further, the number and percentage of participants deemed to have worsening disease will be included. Worsening disease is defined as loss of 15 or more ETDRS letters of vision compared to baseline OR a ≥ 1-step increase in the logOCT scale. This table will be based on the enrolled population. Data will be presented by treatment arm.

Participant flow as outlined in Figure 1 will also be presented.

If a participant terminates from the study at Month 12 but completes the ophthalmic assessments at the Month 12 visit, they will be counted as having completed follow-up through Month 12. Similarly, if a participant discontinues IP or is deemed to have worsening disease at the Month 12 visit, the event will be considered to have occurred after Month 12.

6.0 PARTICIPANT CHARACTERISTICS

These presentations will be based on the enrolled population.

6.1 Participant Demographics

Demographic charteristics collected include baseline age, sex, race and ethnicity. Demographic data will be summarized by treatment as outlined in Table 2 and listed in Listing 1. This table will be based on the enrolled population. The listing will include the registration date of participants as well as the eye that was selected to be the study eye and the treatment to which participants were randomized.

6.2 Medical and Ophthalmic History

The total number and percentage of participants with a history of medical and ocular conditions, medications, and ocular procedures will be summarized. History of ocular conditions and procedures will also be summarized by eye (study eye and fellow eye) and treatment (Table 3). Medical and ocular history will also be listed; the listing will include the date of diagnosis and/or time since diagnosis at baseline for select conditions and procedures.

Any findings from the physical examination at baseline will be included in a listing.

7.0 PARTICIPANT COMPLIANCE

These presentations will be based on the enrolled population.

7.1 Protocol Deviations and Unanticipated Problems

The total number of protocol deviations and unanticipated problems and the number and percentage of participants with deviations and unanticipated problems will be summarized. The number of events per participant and type (serious or not serious) and outcome of events will also be summarized (Table 4). Listings of participant specific and non-participant specific protocol deviations and unanticipated problems will be presented.

7.1.1 IP Compliance Deviations

This listing will present the number of doses taken, the number of doses missed, the expected number of doses taken, and the compliance rates for each participant (Listing 2). For each participant, the number of expected overall doses will be calculated as follows:

$$N_{\,Doses\ expected} = \left(Date_{\,Last\ study\ visit\ attended} - Date_{\,First\ date\ IP\ dispensed}\right) * 2$$

If participants took IP on the date they withdrew from the study or completed the study, the number of expected doses overall will be calculated as follows:

$$N_{\,Doses\ expected} = \left(Date_{\,Last\ study\ visit\ attended} - Date_{\,First\ date\ IP\ dispensed} + 1\right) * 2$$

The site will report the number of pills taken based on self-reported information as recorded in the pill diary. The number of doses taken and missed will be calculated for each participant as:

$$N_{\,Doses\ taken} = N_{Pills\ dispensed} - N_{Pills\ returned}$$

$$N_{Doses\ missed} = N_{Doses\ expected} - N_{Doses\ taken}$$

Negative values will indicate participants who took excess IP.

Compliance rates will be calculated as:

$$Compliance\ rate = (N_{Doses\ taken}/N_{Doses\ expected}) * 100$$

When IP compliance cannot be determined for a participant during any visit due to missing capsule counts, IP compliance will be imputed by taking the median of all available capsule counts recorded at previous study visits.

Participants with compliance rates less than 80% will be flagged.

7.2 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 by participant, procedure and collectively for all participants, cumulatively throughout the study (Table 5). Number of procedures not completed is defined when the site reports a missed procedure or when the protcol monitors note a missed procedure 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:

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

7.3 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 6). 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:

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

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

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

8.0 TREATMENT

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

9.0 STOPPING THE STUDY

If a participant meets one of the criteria for stopping the study listed in Section 3.2.3, a listing containing site, participant ID, date of last contact, visit number, reason for termination and comments related to termination will be constructed.

10.0 PRIMARY OUTCOMES ANALYSIS

The primary outcome is the difference in mean change of BCVA, as measured in ETDRS letters, between the placebo and minocycline groups in the study eye at 12 months compared to baseline. BCVA at baseline as well as change from baseline at Month 12 will be summarized for both treatment arms (Table 7). Interval estimates of mean change in BCVA will also be constructed. The difference in mean change between the two groups at Month 12 will be calculated as the mean change from baseline at Month 12 for treatment arm 1 minus the mean change from baseline at Month 12 for treatment arm 2. Manifest refraction values for BCVA will be used when available.

This analysis will be based on the primary analysis population.

Additional presentations stratified by site will be constructed as appropriate.

Exploratory nonparametric statistical analyses will be conducted as appropriate.

Participants who were exposed to recent (< three months) systemic steroid or systemic anti-VEGF prior to enrolling will be analyzed separately as appropriate to assess for any possible confounding effects for treatment benefit.

11.0 SECONDARY OUTCOMES ANALYSIS

These analyses will be based on the safety population who completed the respective visits.

Additional presentations stratified by site will be constructed as appropriate.

Exploratory nonparametric statistical analyses will be conducted as appropriate.

Participants who were exposed to recent (< three months) systemic steroid or systemic anti-VEGF prior to enrolling will be analyzed separately as appropriate to assess for any possible confounding effects for treatment benefit.

11.1 Number of Bevacizumab Injections

The number of bevacizumab injections from baseline to 12 months and from baseline to 24 months will be tabulated by participant (Table 8). Additionally, the average number of injections between baseline and Months 12 and 24 will be calculated for each treatment arm, and the difference in the number of injections between the two groups will be presented (Table 9). The difference in the number of injections between the two groups will be calculated as the number of injections in treatment arm 1 minus the number of injections in treatment arm 2.

11.2 Macular Sensitivity

Mean change in macular sensitivity in the study eye, as measured by microperimetry, from baseline at Months 3, 6, 12, 18 and 24 will be summarized by treatment arm (Table 10). The difference in mean macular sensitivity between the two groups will also be presented. The mean difference in macular sensitivity between the two groups at a visit will be calculated as the mean change from baseline in treatment arm 1 minus the mean change from baseline in treatment arm 2.

11.3 Best-Corrected Visual Acuity (BCVA)

The mean change in ETDRS BCVA of the study eye at 24 months compared to baseline will be analyzed similar to the primary outcome detailed in section 10.0 (Table 11). Manifest refraction values for BCVA will be used when available.

11.4 Optical Coherence Tomography (OCT)

The changes in retinal thickness in the study eye, as measured by OCT, at 6, 12, 18 and 24 months compared to baseline will be summarized by treatment arm, and interval estimates of the mean change will be constructed (Table 12). The difference in retinal thickness between the two groups will also be presented. The difference in retinal thickness between the two groups at a visit will be calculated as the mean change from baseline in treatment arm 1 minus the mean change from baseline in treatment arm 2.

11.5 Improvement of ≥ 1 logOCT Scale Step

The number of participants improving ≥ 1 logOCT scale step at 12 and 24 months compared to baseline in the study eye will be presented by treatment arm (Table 13). The difference in the number of participants improving ≥ 1 logOCT scale step from baseline will be calculated as the number of participants improving in treatment arm 1 minus the number of participants improving in treatment arm 2. Improvement of ≥ 1 logOCT scale step is defined as a decrease of ≥ 1-step on the logOCT scale, where

$$Change\ in\ logOCT = \log(followup\ thickness/300) - \log(baseline\ thickness/300).$$

A decrease in one-step is considered clinically significant (7). A one-step decrease is equivalent to at least a 20% improvement of central macular thickness and represents greater than twice the variability of retinal thickness measurements (approximately 25-30 microns). The table below presents examples of OCT measurements with their corresponding LogScore, where

$$LogScore = 10 * \log(OCT).$$

OCT and Corresponding LogScores (7)

LogScore	OCT (µm)
0	300
0.5	337
1	378
1.5	424
2	475
2.5	533
3	599
3.5	672
4	754
4.5	846
5	949
5.5	1064
6	1194
6.5	1340

11.6 Changes in Fluid Leakage

Changes in the fluid leakage in the macula of the study eye, as demonstrated by fluorescein angiography, at 12 and 24 months compared to baseline will be summarized by treatment arm (Table 14). The difference in changes in fluid leakage between the two groups will also be

presented as the change in fluid leakage in treatment arm 1 minus the change in fluid leakage in treatment arm 2.

12.0 SAFETY ANALYSIS

These analyses will be based on the safety population, unless otherwise specified. All relevant information will be listed; data for all enrolled participants will be included in the listings. Relevant data may be plotted against time.

Additional presentations stratified by site will be constructed as appropriate.

12.1 Adverse Events (AEs)

All AEs reported will be summarized by treatment arm and overall. Total number and percentage of particpants with AEs will be presented by severity, ocular specification, outcome, and relation to IP (Table 15). AEs will also be summarized by system organ class (SOC) and preferred term (PT) (Table 16). If sufficient data is present, summaries similar to Table 15 and Table 16 will be generated for all serious adverse events (SAEs), and summaries similar to Table 16 will be presented for natural progression of the disease events.

All AEs and events corresponding to natural progressions of the disease will be listed.

12.2 Withdrawal from IP Due to Vision Loss and Adverse Events and Participants with Worsening Disease

Participants who discontinue IP due to vision loss and adverse events will be summarized in Table 1. Participants who are deemed to have worsening disease at any point during follow-up will also be presented in Table 1. Worsening disease is defined as a loss of 15 or more ETDRS letters of vision compared to baseline OR as 1-step increase in the logOCT scale.

12.3 Best-Corrected Visual Acuity

Visual acuity will be collected at baseline and all follow-up visits for both eyes. Total letters read at each visit and change from baseline at each follow-up visit will be presented overall and by treatment arm for both the study and fellow eyes in Table 17. The number and percentage of participants with ≥ 10 letter change at each visit will also be included. Manifest refraction values for BCVA will be used when available.

Mean BCVA will be plotted over time for the minocycline and placebo treatment arms for both the study and fellow eyes (Figure 2). Individual BCVA will also be plotted over time for both eyes (Figure 3).

12.4 Optical Coherence Tomography (OCT)

Central retinal thickness, as measured by OCT, is assessed at all visits for both eyes. Central retinal thickness and change from baseline at each follow-up visit will be presented overall and by treatment arm for the study and fellow eyes in Table 18.

Mean central retinal thickness will be plotted over time for the minocycline and placebo treatment arms for both the study and fellow eyes (Figure 4). Individual central retinal thickness will also be plotted over time for both eyes (Figure 5).

12.5 Intraocular Pressure (IOP)

Intraocular pressure (IOP) is assessed at all visits for both eyes. IOP measurements at each visit and change from baseline at each follow-up visit will be summarized using descriptive statistics and will be presented overall and by treatment arm for both the study and fellow eyes (Table 19).

12.6 Thyroid Palpation Assessment and Review of Systems

A thyroid palpation assessment and a review of systems are completed at every visit. The number and percentage of participants with clinically significant thyoid palpation findings will be summarized overall and by treatment arm (Table 20). The number and percentage of participants who experienced dizziness, sun sensitivity, or diarrhea between visits will also be summarized in Table 20.

12.7 Laboratory Assessments

An acute care panel, hepatic panel and thyroid function testing will be performed at baseline, Month 2 and every four months thereafter (Months 6, 10, 14, 18 and 22), as well as the final visit at Month 24. Frequency and percentage of participants reporting laboratory abnormalities at baseline will be summarized with shift from baseline to each follow-up visit (Table 21).

12.8 Other Safety Outcomes

Exploratory analyses and/or descriptive summary statistics of color fundus photography (CFP), fluorescein angiogram (FA), microperimetry and other assessments will be performed as appropriate.

13.0 Quality Assurance Plans

To ensure accurate, reliable study results, two statisticians will separately analyze and compare the primary study outcome. 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.

14.0 References

1. Mitchell P, Smith W, Chang A. Prevalence and associations of retinal vein occlusion in Australia. The Blue Mountains Eye Study. Archives of ophthalmology 1996; 114(10): 1243-1247.
2. Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion: the Beaver Dam Eye Study. Transactions of the American Ophthalmological Society 2000; 98: 133-141; discussion 141-133.
3. Zemke D, Majid A. The potential of minocycline for neuroprotection in human neurologic disease. Clin Neuropharmacol 2004; 27(6): 293-298.
4. Tikka T, Fiebich BL, Goldsteins G, Keinanen R, Koistinaho J. Minocycline, a tetracycline derivative, is neuroprotective against excitotoxicity by inhibiting activation and proliferation of microglia. J Neurosci 2001; 21(8): 2580-2588.
5. Bosco A, Inman DM, Steele MR et al. Reduced retina microglial activation and improved optic nerve integrity with minocycline treatment in the DBA/2J mouse model of glaucoma. Investigative ophthalmology & visual science 2008; 49(4): 1437-1446.
6. Yang LP, Zhu XA, Tso MO. A possible mechanism of microglia-photoreceptor crosstalk. Molecular vision 2007; 13: 2048-2057.

7. Ferris FL 3rd, Miller KM, Glassman AR, Beck RW; Diabetic Retinopathy Clinical Research Network. A proposed method of logarithmic transformation of optical coherence tomography data for use in clinical research. Ophthalmology. 2010 Aug;117(8): 1512-6.

15.0 MOCK SHELLS

TABLES

Table 1: Participant Disposition

Disposition	Treatment Arm 1 (N=X)[1]	Treatment Arm 2 (N=X)[1]	Total (N=X)[1]
Enrolled	x (x%)	x (x%)	x (x%)
Completed Follow-up Through Month 12	x (x%)	x (x%)	x (x%)
Completed Study	x (x%)	x (x%)	x (x%)
Completed Follow-up	x (x%)	x (x%)	x (x%)
Terminated per protocol	x (x%)	x (x%)	x (x%)
Discontinued IP Early	x (x%)	x (x%)	x (x%)
Prior to Month 12	x (x%)	x (x%)	x (x%)
After Month 12	x (x%)	x (x%)	x (x%)
Reason			
Participant non-compliance	x (x%)	x (x%)	x (x%)
Safety Withdrawal	x (x%)	x (x%)	x (x%)
Vision loss[2]	x (x%)	x (x%)	x (x%)
AEs[3]	x (x%)	x (x%)	x (x%)
Other	x (x%)	x (x%)	x (x%)
Discontinued Study Early	x (x%)	x (x%)	x (x%)
Prior to Month 12	x (x%)	x (x%)	x (x%)
After Month 12	x (x%)	x (x%)	x (x%)
Reason			
AE/intercurrent illness	x (x%)	x (x%)	x (x%)
Death	x (x%)	x (x%)	x (x%)
Requested termination	x (x%)	x (x%)	x (x%)
Other	x (x%)	x (x%)	x (x%)
Deemed to Have Worsening Disease[4]	x (x%)	x (x%)	x (x%)
Prior to Month 12	x (x%)	x (x%)	x (x%)
After Month 12	x (x%)	x (x%)	x (x%)

[1] Column header counts and denominators are the number of participants in the enrolled population in each treatment arm and overall. Percentages are rounded to the nearest whole number.
[2] Manually identified based on investigator's comments for those participants with reason for withdrawal from IP as "safety withdrawal".
[3] Participants with reason for withdrawal from IP indicated as "safety withdrawal" for the occurrence of AEs assessed as being related to the study IP that preclude further administration of IP.
[4] Worsening disease is defined as a loss of 15 or more ETDRS letters of vision compared to baseline OR a 1-step increase in the logOCT scale.

Table 2: Demographic Information by Treatment Arm

Demographic Characteristics	Treatment Arm 1 (N=X)[1]	Treatment Arm 2 (N=X)[1]	Total (N=X)[1]
Gender N (%)			
Female	x (x%)	x (x%)	x (x%)
Male	x (x%)	x (x%)	x (x%)
Age Category (years) at Baseline N (%)			
56-60	x (x%)	x (x%)	x (x%)
61-65	x (x%)	x (x%)	x (x%)
66-70	x (x%)	x (x%)	x (x%)
71-75	x (x%)	x (x%)	x (x%)
76-80	x (x%)	x (x%)	x (x%)
81-85	x (x%)	x (x%)	x (x%)
Age (years) at Baseline			
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)
Ethnicity N (%)			
Hispanic or Latino	x (x%)	x (x%)	x (x%)
Not Hispanic or Latino	x (x%)	x (x%)	x (x%)
Race N (%)			
Black	x (x%)	x (x%)	x (x%)
White	x (x%)	x (x%)	x (x%)
Unknown	x (x%)	x (x%)	x (x%)

[1] Column header counts and denominators are the number of participants in the enrolled population in each treatment arm and overall. Percentages are rounded to the nearest whole number.

Table 3: Medical and Ocular History

	Treatment Arm 1			Treatment Arm 2			Total		
Conditions/Procedures	**Study Eye (N=X)[1]**	**Fellow Eye (N=X)[1]**	**Total (N=X)[1,2]**	**Study Eye (N=X)[1]**	**Fellow Eye (N=X)[1]**	**Total (N=X)[1,2]**	**Study Eye (N=X)[1]**	**Fellow Eye (N=X)[1]**	**Total (N=X)[1,2]**
Any Medical Condition			x (x%)			x (x%)			x (x%)
Renal disease			x (x%)			x (x%)			x (x%)
Hepatitis			x (x%)			x (x%)			x (x%)
Liver Failure			x (x%)			x (x%)			x (x%)
…									
Any Medication History			x (x%)			x (x%)			x (x%)
Systemic anti-VEGF			x (x%)			x (x%)			x (x%)
Systemic steroid			x (x%)			x (x%)			x (x%)
Any Ocular Condition	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Recurrent RVO	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
RVO present > 18 months	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Any Ocular Procedure	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Intravitreal steroid injection	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Cataract surgery	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Vitrectomy	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
…									

[1] Column header counts and denominators are the number of participants in the enrolled population in each treatment arm and overall. Percentages are rounded to the nearest whole number.
[2] If a participant reported an ocular condition or procedure in both eyes, the participant will only be counted once.

Table 4: Protocol Deviations and Unanticipated Problems

	Participant-Specific		Non-Participant Specific	Total
	Number of Events	Number of Participants with Events (N=X)[1]	Number of Events	Number of Events
All Events	x	x (x%)	x	x
Protocol Deviations	x	x (x%)	x	x
Unanticipated Problems	x	x (x%)	x	x
Number of Events per Participant				
N	x			
Mean (SD)	x.x (x.x)			
Median	x			
Range (Min, Max)	x, x			
Type				
Serious	x	x (x%)	x	x
Not serious	x	x (x%)	x	x
Outcome				
Participant follow-up continues	x	x (x%)	x	x
Participant follow-up terminated	x	x (x%)	x	x
…	x	x (x%)	x	x

[1] Column header count and denominators are the number of participants in the enrolled population. Percentages are rounded to the nearest whole number.

Table 5: Missed Study Procedures

Category	Participant ID/ Procedure	Number of Expected Procedures	Number of Missed Procedures	Percentages of Missed Procedures
Participant	001	xx	xx	x.x
	002	xx	xx	x.x
	003	xx	xx	x.x
	…	xx	xx	x.x
	…	xx	xx	x.x
Procedure	Acute Care Panel	xx	xx	x.x
	Adverse Event Assessment	xx	xx	x.x
	BCVA (ETDRS)	xx	xx	x.x
	…	xx	xx	x.x
	…	xx	xx	x.x
Total		**xx**	**xx**	**x.x**

Table 6: Missed and Out of Window Study Visits

Participant ID	Number of Expected Visits	Number of Missed Visits	Percentage of Missed Visits	Number of Out of Window Visits	Percentage of Out of Window Visits	Visits Missed or Out of Window
001	xx	xx	x.x	xx	x.x	xxx
002	xx	xx	x.x	xx	x.x	
…	xx	xx	x.x	xx	x.x	
Total	xx	xx	x.x	xx	x.x	

Table 7: Analysis of Primary Outcome of Change in BCVA of the Study Eye from Baseline at Month 12

	Treatment Arm 1		Treatment Arm 2		Difference[1]	
Visit	**BCVA (letters read)**	**Δ (letters read)**	**BCVA (letters read)**	**Δ (letters read)**	**BCVA (letters read)**	**Δ (letters read)**
Baseline						
N	x		x			
Mean (SD)	x (x)		x (x)		x (x)	
95% Confidence Interval	(x, x)		(x, x)		(x, x)	
Month 12						
N	x	x	x	x		
Mean (SD)	x (x)	x (x)	x (x)	x (x)	x (x)	**x (x)**
95% Confidence Interval	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	**(x.x, x.x)**

Δ indicates change from baseline.

[1] Difference is defined as Treatment Arm 1 – Treatment Arm 2. Negative values indicate that participants in Treatment Arm 2 experienced a higher visual acuity or a more positive change from baseline at Month 12.

Table 8: Analysis of Secondary Outcome of Number of Bevacizumab Injections by Participant from Baseline to Month 12 and from Baseline to Month 24

Participant ID	Treatment Arm	Visit Period	Number of Bevacizumab Injections
001	T1/T2	Baseline to Month 12	xx
		Baseline to Month 24	xx
002	T1/T2	Baseline to Month 12	xx
		Baseline to Month 24	xx
…	…	…	…

Table 9: Analysis of Secondary Outcome of Summary of Bevacizumab Injections by Treatment Arm from Baseline to Month 12 and from Baseline to Month 24

Visit Period	Treatment Arm 1 (N=X)[1]	Treatment Arm 2 (N=X)[1]	Difference[2]
Baseline to Month 12			
Number of Injections	xx	xx	xx
Mean	x.x	x.x	x.x
Baseline to Month 24			
Number of Injections	xx	xx	xx
Mean	x.x	x.x	x.x

[1] Column header counts are the number of participants in the safety population in each treatment arm and overall.
[2] Difference is defined as Treatment Arm 1 – Treatment Arm 2. Negative values indicate that participants in Treatment Arm 2 received more injections during the respective visit period.

Table 10: Analysis of Secondary Outcome of Change in Macular Sensitivity as Measured by Microperimetry from Baseline at Months 3, 6, 12, 18 and 24

This table will be similar to Table 7. The rows corresponding to the 95% confidence interval will be excluded.

Table 11: Analysis of Secondary Outcome of Change in BCVA of the Study Eye from Baseline at Month 24

This table will be similar to Table 7.

Table 12: Analysis of Secondary Outcome of Change in Central Retinal Thickness of the Study Eye from Baseline at Months 6, 12, 18 and 24

This table will be similar to Table 7.

Table 13: Analysis of Secondary Outcome of Number of Participants Improving ≥ 1 logOCT Scale Step in the Study Eye at 12 and 24 Months Compared to Baseline

Visit	Treatment Arm 1 N (%)[1]	Treatment Arm 2 N (%)[1]	Difference[2]
Month 12	x (x%)	x (x%)	x
Month 24	x (x%)	x (x%)	x

[1] Denominators are the number of participants in the safety population in each treatment arm and overall. Percentages are rounded to the nearest whole number.
[2] Difference is defined as Treatment Arm 1 – Treatment Arm 2. Negative values indicate that more participants in Treatment Arm 2 improved by ≥ 1 logOCT scale step at the respective visit compared to baseline.

Table 14: Analysis of Secondary Outcome of Change in Fluid Leakage in the Macula in the Study Eye at 12 and 24 Months Compared to Baseline

Visit	Treatment Arm 1 N (%)[1]	Treatment Arm 2 N (%)[1]	Difference[2]
Month 12			
Increase	x (x%)	x (x%)	x
Decrease	x (x%)	x (x%)	x
No Change	x (x%)	x (x%)	x
Month 24			
Increase	x (x%)	x (x%)	x
Decrease	x (x%)	x (x%)	x
No Change	x (x%)	x (x%)	x

[1] Denominators are the number of participants in the safety population in each treatment arm and overall. Percentages are rounded to the nearest whole number.
[2] Difference is defined as Treatment Arm 1 – Treatment Arm 2. Negative values indicate that more participants in Treatment Arm 2 experienced a certain change in fluid leakage at the respective visit compared to baseline.

Table 15: Summary of Adverse Events

	Treatment Arm 1		Treatment Arm 2		Total	
	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
All AEs	x (x%)	x	x (x%)	x	x (x%)	x
Serious Adverse Events	x (x%)	x	x (x%)	x	x (x%)	x
Severity						
Mild	x (x%)	x	x (x%)	x	x (x%)	x
Moderate	x (x%)	x	x (x%)	x	x (x%)	x
Severe	x (x%)	x	x (x%)	x	x (x%)	x
Life-threatening	x (x%)	x	x (x%)	x	x (x%)	x
Death	x (x%)	x	x (x%)	x	x (x%)	x
Eye						
Non-ocular	x (x%)	x	x (x%)	x	x (x%)	x
Study eye	x (x%)	x	x (x%)	x	x (x%)	x
Fellow eye	x (x%)	x	x (x%)	x	x (x%)	x
Outcome						
Resolved	x (x%)	x	x (x%)	x	x (x%)	x
Resolved with sequalae	x (x%)	x	x (x%)	x	x (x%)	x
Death	x (x%)	x	x (x%)	x	x (x%)	x
Resolved by convention	x (x%)	x	x (x%)	x	x (x%)	x
Relation to IP						
Yes	x (x%)	x	x (x%)	x	x (x%)	x
No	x (x%)	x	x (x%)	x	x (x%)	x

[1] Denominators are the number of participants in the safety population in each treatment arm and overall. Percentages are rounded to the nearest whole number.

Table 16: Summary of Adverse Events by System Organ Class (SOC) and Preferred Term (PT)

System Organ Class/ Preferred Term	Treatment Arm 1		Treatment Arm 2		Total	
	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
SOC1	x (x%)	x	x (x%)	x	x (x%)	x
PT1	x (x%)	x	x (x%)	x	x (x%)	x
PT2	x (x%)	x	x (x%)	x	x (x%)	x
SOC2	x (x%)	x	x (x%)	x	x (x%)	x
PT1	x (x%)	x	x (x%)	x	x (x%)	x
PT2	x (x%)	x	x (x%)	x	x (x%)	x
…						
…						

[1] Denominators are the number of participants in the safety population in each treatment arm and overall. Percentages are rounded to the nearest whole number.

Table 17: Summary of Visual Acuity Over Time

	Treatment Arm 1				Treatment Arm 2				Total			
	BCVA (letters read)		Δ (letters read)		BCVA (letters read)		Δ (letters read)		BCVA (letters read)		Δ (letters read)	
Visit	**Study Eye**	**Fellow Eye**	**Study Eye**	**Fellow Eye**	**Study Eye**	**Fellow Eye**	**Study Eye**	**Fellow Eye**	**Study Eye**	**Fellow Eye**	**Study Eye**	**Fellow Eye**
Baseline												
N	x	x			x	x			x	x		
Median	x.x	x.x			x.x	x.x			x.x	x.x		
Mean (SD)	x (x)	x (x)			x (x)	x (x)			x (x)	x (x)		
(Min, Max)	(x, x)	(x, x)			(x, x)	(x, x)			(x, x)	(x, x)		
Month 1												
N	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	x.x	x.x	x.x	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)
(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)
Change of ≥ 10 letters, N(%)[1]		x (x%)		x (x%)		x (x%)		x (x%)		x (x%)		x (x%)
Month 2												
…												
…												
Month 24												
…												

Δ indicates change from baseline.

[1] Denominators are the number of participants in the safety population in each treatment arm and overall with data at the given visit. Percentages are rounded to the nearest whole number.

Table 18: Summary of Central Retinal Thickness Over Time

This table will be similar to Table 17. The row corresponding to Change of ≥ 10 letters will be excluded.

Table 19: Summary of IOP Over Time

This table will be similar to Table 17. The row corresponding to Change of ≥ 10 letters will be excluded.

Table 20: Results of Thyroid Palpation Assessment and Review of Systems Over Time

	Treatment Arm 1				Treatment Arm 2				Total			
	Significant Findings	Review of Systems			Significant Findings	Review of Systems			Significant Findings	Review of Systems		
Visit	Thyroid Palpation	Dizziness	Sun Sensitivity	Diarrhea	Thyroid Palpation	Dizziness	Sun Sensitivity	Diarrhea	Thyroid Palpation	Dizziness	Sun Sensitivity	Diarrhea
Baseline	x (x%)				x (x%)				x (x%)			
Month 1	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Month 2	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%)	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%)
Month 24	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)

Denominators are the number of participants in the safety population in each treatment arm and overall with data at the given visit. Percentages are rounded to the nearest whole number.

Table 21: Summary of Laboratory Assessments Over Time

	Treatment Arm 1				Treatment Arm 2				Total			
Visit	Participants with Lab Assessments N[1]	Abnormal Lab Assessments N (%)[2]	Any Δ N (%)[2]	Clinically Significant Δ N (%)[2]	Participants with Lab Assessments N[1]	Abnormal Lab Assessments N (%)[2]	Any Δ N (%)[2]	Clinically Significant Δ N (%)[2]	Participants with Lab Assessments N[1]	Abnormal Lab Assessments N (%)[2]	Any Δ N (%)[2]	Clinically Significant Δ N (%)[2]
Baseline	x	x (%)			x	x (%)			x	x (%)		
Month 2	x		x (%)	x (%)	x		x (%)	x (%)	x		x (%)	x (%)
Month 6	x		x (%)	x (%)	x		x (%)	x (%)	x		x (%)	x (%)
Month 10	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 (%)
Month 22	x		x (%)	x (%)	x		x (%)	x (%)	x		x (%)	x (%)
Month 24	x		x (%)	x (%)	x		x (%)	x (%)	x		x (%)	x (%)

Δ indicates changes from baseline

[1] Participants in the safety population in each treatment arm and overall with laboratory assessment data at the given visit.

[2] Denominators are the number of participants in the safety population in each treatment arm and overall with laboratory assessment data at the given visit.

FIGURES

Figure 1: Consort Diagram

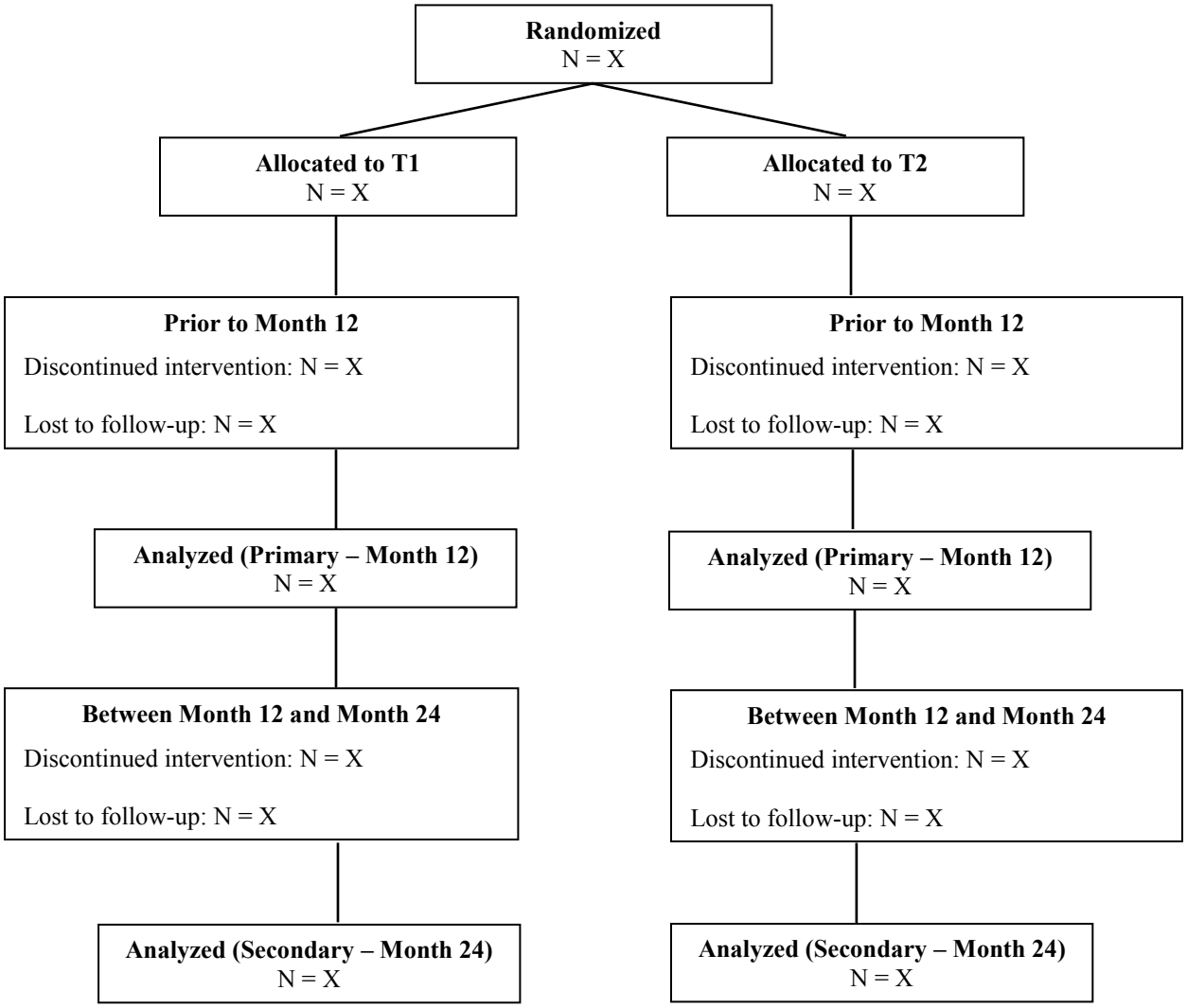

Figure 2: Mean Best-Corrected Visual Acuity Over Time by Treatment Arm

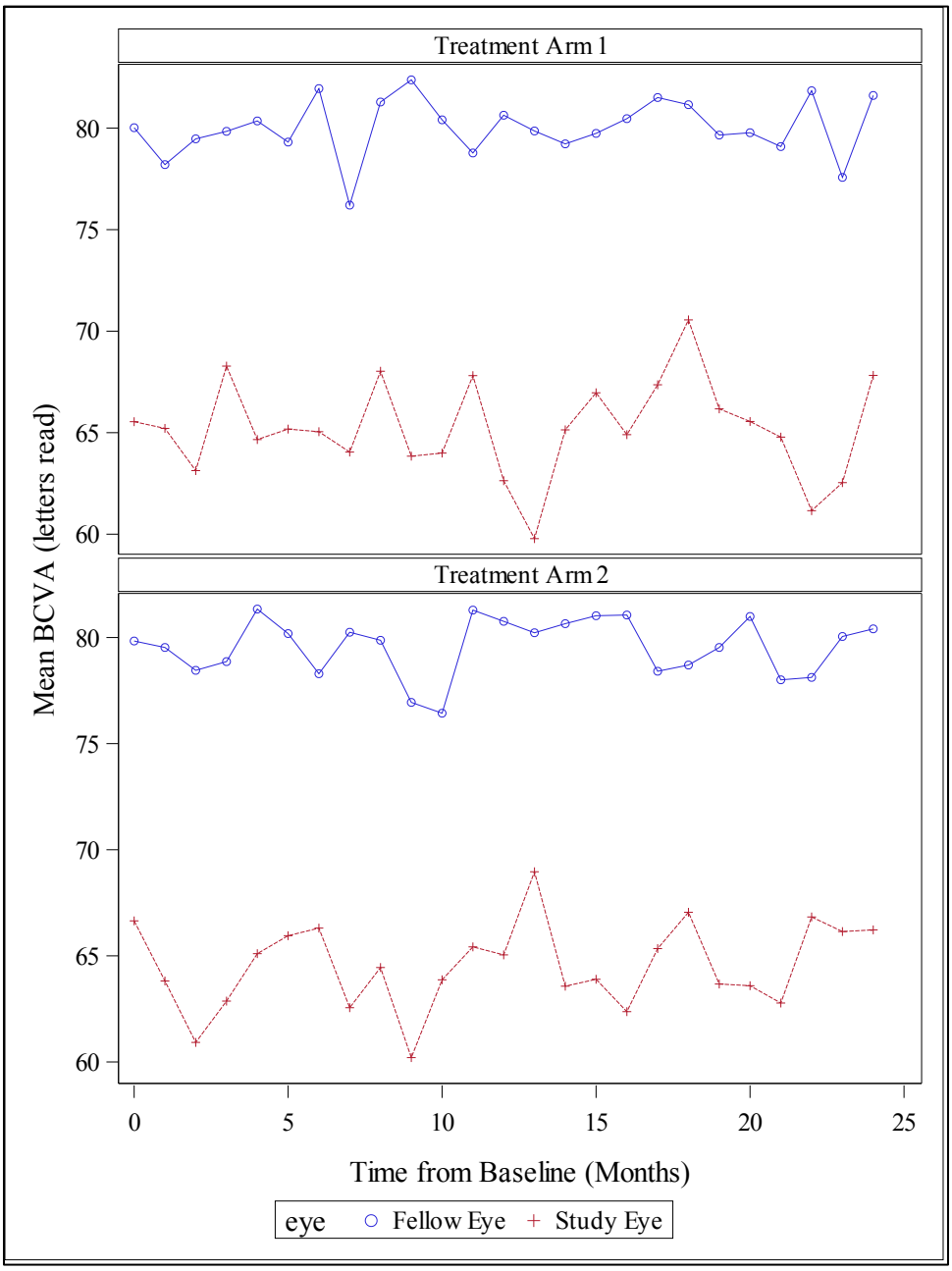

Figure 3: Best-Corrected Visual Acuity Over Time by Participant

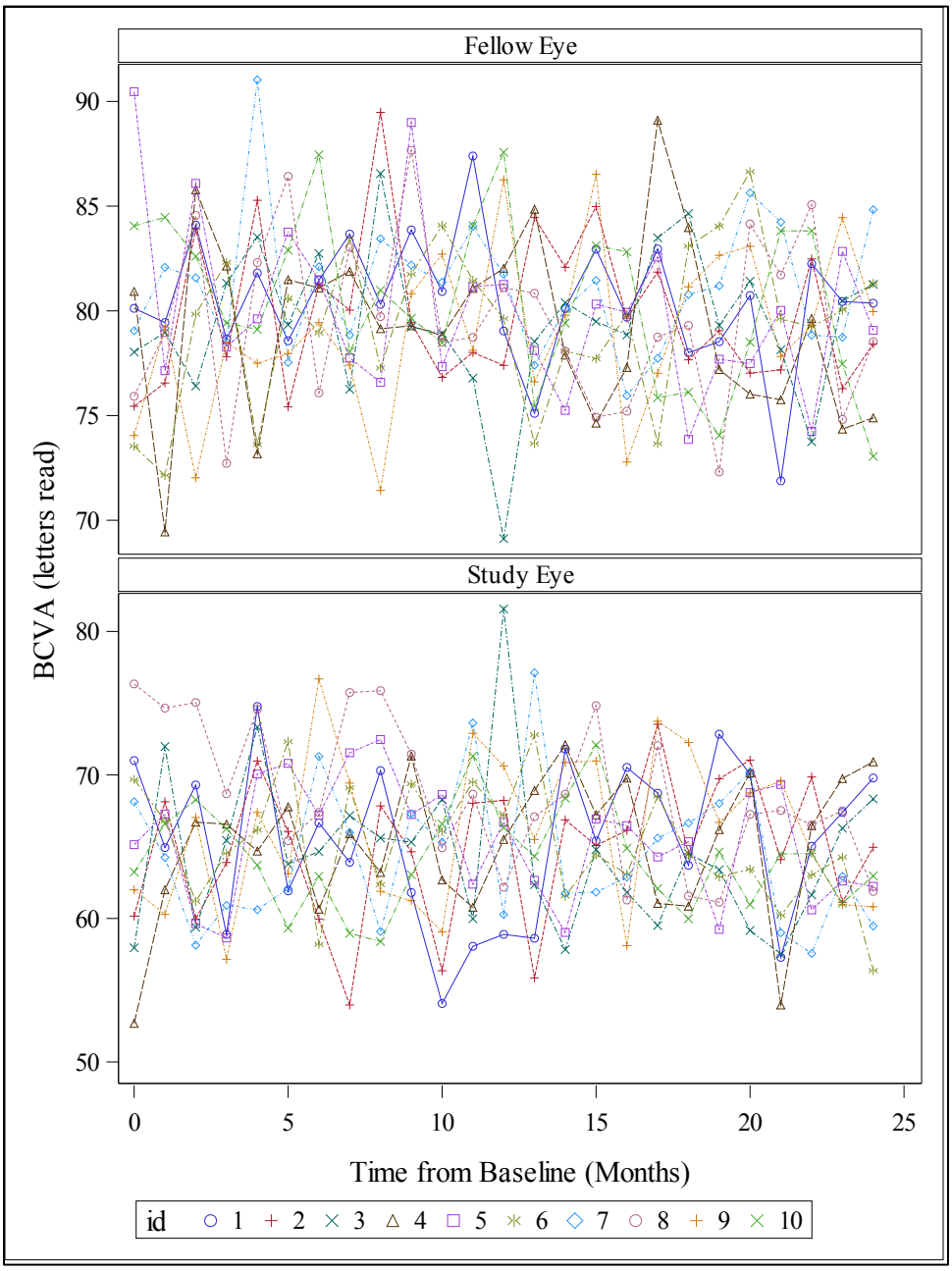

Figure 4: Mean Central Retinal Thickness Over Time by Treatment Arm

This figure will be similar to Figure 2.

Figure 5: Central Retinal Thickness Over Time by Participant

This figure will be similar to Figure 3.

LISTINGS

Listing 1: Demographic Information by Participant

Participant ID	Treatment Arm	Registration Date	Study Eye	Age	Gender	Race	Ethnicity
001	xx	mm/dd/yy	xx	xx	xxx	xxx	xxx
002	xx	mm/dd/yy	xx	xx	xxx	xxx	xxx
…	xx	mm/dd/yy	xx	xx	xxx	xxx	xxx

Listing 2: IP Compliance

Participant ID	Treatment Arm	Number of Doses Taken	Number of Doses Missed	Expected Number of Doses Taken	Compliance Rate (%)
001	xx	xx	xx	xx	x.x
002	xx	xx	xx	xx	x.x
…	xx	xx	xx	xx	x.x