Statistical Analysis Plan

For

An Investigation of Vitamin A Palmitate Supplementation in Patients with Age-Related Macular Degeneration (and Without Reticular Pseudodrusen) and Delayed Dark Adaptation

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VERSION HISTORY

Version/Date	Changes
1.0/27JUL2021	***Initial Document***
2.0/18DEC2023	***Title Page:*** Updated Principal Investigator; ***List of Abbreviations:*** Updated for currency; ***Section 1.0:*** Updated protocol version and date; ***Section 2.0:*** Updated "Advantage EDC" to "Advantage eClinical®"; ***Section 3.3.1.1:*** Updated inclusion criterion corresponding to the number of acceptable methods of contraception**;** ***Section 5.2:*** Updated to clarify that exploratory analyses are based on the primary analysis population; ***Section 5.7:*** Removed Graphpad Prism from utilized software; ***Section 11.2:*** Excluded fellow eye from statistical model results for LLVA; ***Section 12.1:*** Added "outcome" to AE table summary; ***Section 13.2:*** Updated to clarify that abnormal results from laboratory assessments preformed at Screening are reported at Baseline; ***Section 14.6:*** Added summary of vitamin A palmitate consumption; ***Section 14.7:*** Updated to clarify that Presence of RPD is assessed at Baseline; ***Section 18.0:*** Made applicable corresponding updates described above to mock shells. Additionally, added continuous age summary in Table 2; added assessment for Coumadin in Table 3; updated placement of statistical results and inclusion of covariance structure in Table 9, Table 10, and Table 11; and updated reported decimal places for LLQ values. General updates throughout document to ensure consistency of abbreviations.

List of Abbreviations

Abbreviation	Term
AE	Adverse Event
AMD	Age-related Macular Degeneration
BCVA	Best-Corrected Visual Acuity
CC	Clinical Center
CTCAE	Common Terminology Criteria for Adverse Events
EMR	Electronic Medical Record
ETDRS	Early Treatment Diabetic Retinopathy Study
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
IU	International Unit
LLQ	Low luminance questionnaire
LLVA	Low luminance visual acuity
LORD	Late-onset retinal disease
NEI	National Eye Institute
NIH	National Institutes of Health
PSC	Posterior Subcapsular Cataract
PT	Preferred Term
RIT	Rod Intercept Time
RPD	Reticular Pseudodrusen
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
YAG	Yttrium-Aluminum Garnet

1.0 INTRODUCTION

This statistical analysis plan (SAP) provides the proposed analyses for DA VitA AMD protocol titled "An Investigation of Vitamin A Palmitate Supplementation in Patients with Age-Related Macular Degeneration (and Without Reticular Pseudodrusen) and Delayed Dark Adaptation". This document contains 18 sections: (1) background of the study, (2) data sources for analyses, (3) an overview of the study design, (4) definitions, (5) statistical considerations, (6) participant disposition, (7) participant characteristics, (8) participant compliance, (9) statistical analysis for the primary outcome, (10) statistical analyses for secondary outcomes, (11) exploratory analyses (12) safety outcomes, (13) other safety outcomes, (14) other ophthalmic assessments, (15) rationale for deviation from pre-specified analysis plan, (16) quality assurance plan, (17) references, and (18) mock shells for proposed tables, listings, and figures. This document is based on version 9.0 of the protocol dated September 25, 2023. Any deviation from this SAP, not outlined in Section 15.0, will be described and justified in protocol amendments and/or in the final study report, as appropriate.

1.1 Age-related Macular Degeneration (AMD) and Scientific Rationale for the Study

Age-related macular degeneration (AMD) has been the leading cause of central vision loss in people aged 65 or older in developed countries[1,2]. Decreases in central vision from late AMD is well-established, and even intermediate AMD can display small but statistically significant reductions in central acuity compared with those without AMD[3-5]. However, earlier cell changes accompanying AMD have direct links to additional measures of retinal function. Histopathological examination of eyes from patients with AMD has demonstrated preferential loss of rods in the photoreceptor layer of the retina with cones persisting as the last surviving photoreceptors[6-8]. Studies employing multiple approaches to measure rod and cone function have documented preferential reduced rod function in eyes with AMD[9-14] A focal dark adaptometer able to focus on areas 0.5 to 3 mm from the fovea, areas thought to have earliest rod loss, has demonstrated impairments in eyes with non-advanced AMD compared to older eyes without AMD, even when visual acuity varied little between severity groups[11]. Increasing AMD severity

was associated with increased rod intercept time (RIT), an outcome of dark adaptation, with eyes having reticular pseudodrusen (RPD) demonstrating the most significant delays[11].

Interpreting the data on dark adaptation across different phenotypes of macula, there are several possible hypotheses that have been proposed in the literature. A testable hypothesis proposed in the literature is that the sub-RPE (retinal pigment epithelium) deposits act as diffusion barriers for entry of sufficient vitamin A into the photoreceptors. This would lead to a local deficiency or a form of nutritional deprivation at the level of the photoreceptor. Vitamin A deficiency has long been known to cause night blindness with rod dysfunction and while these patients are not deficient based on serum levels, there still could be a local deficiency at the level of photoreceptors. Without available vitamin A (due to a serum deficiency or local deficiency) to combine with opsin, photoreceptors cannot regenerate functional visual pigment at the normal rate after light exposure leading to a slowing of dark adaptation.

A first step in understanding the pathophysiology identified by abnormal dark adaptation would be to supplement eyes with abnormal dark adaptation with vitamin A palmitate. Restoration or improvement of visual function while on supplemental vitamin A palmitate would provide data to support this hypothesis in the setting of AMD. Jacobson et al[15] tested this hypothesis in patients with Sorsby's fundus dystrophy and demonstrated that vitamin A palmitate supplementation could restore dark adaptation in these patients using 50,000 international unit (IU) vitamin A palmitate for one month, but was also able to show maintenance of some (but not all) aspects of dark adaptation with 5,000 IU vitamin A palmitate[15]. Ayyagari and Sieving et al[16] demonstrated that the dark adaptation of patients with late-onset retinal disease (LORD) with mutations in CTRP5 could be shifted with 15,000 IU vitamin A palmitate within two months of supplementation. Owsley et al[17] initiated investigation into this question in older adults with early AMD, and the results demonstrated that a short-term, high-dose course of preformed vitamin A increased the rate of rod-mediated dark adaptation. However, this hypothesis could be investigated with greater depth using more refined fundus phenotyping and psychophysical testing.

The preliminary analysis of the data from Cohort 1 in the DA VitA study showed that 16,000 IU of vitamin A palmitate per day was well tolerated with no adverse events (AEs) requiring discontinuation of the study product. Given the previously demonstrated efficacy of vitamin

A palmitate supplementation in the treatment of Sorsby's fundus dystrophy[15] and eyes with early AMD[17], the introduction of a second cohort that will take an increased dose of vitamin A palmitate (48,000 IU per day) in the DA VitA study is necessary since the data show that Cohort 1 did not present significant improvement in dark adaptation after taking 16,000 IU per day. The knowledge gained would provide further insights into pathogenesis of age-related macular degeneration.

2.0 DATA SOURCE

Data will be received from the National Eye Institute (NEI) via their electronic data capture system (Electronic Medical Record, EMR), which will then be uploaded daily to the Coordinating Center's (CC) database, Advantage eClinical®. Medmont and AdaptDx kinetic measures (i.e., curve parameters) and Medmont pre-bleach thresholds will be collected and analyzed at the NEI and will not be entered into EMR or transferred to the CC. All other analyses described in this document will be performed by the CC.

3.0 GENERAL REVIEW OF STUDY DESIGN

3.1 Study Design

The DA VitA AMD study is a prospective, uncontrolled, single center, pilot study to investigate the potential efficacy and safety of vitamin A palmitate dosing in improving dark adaptation in participants with AMD (without RPD) and abnormal dark adaptation.

The study will require five visits (screening, baseline, Month 1, Month 2, and Month 3) for Cohort 1 and four visits (screening, baseline, Month 1, and Month 2) for Cohort 2. Participants in Cohort 1 will be instructed to take vitamin A palmitate 16,000 IU daily by mouth for two months from baseline through Month 2 and will continue in the study through Month 3. Participants in Cohort 2 will be instructed to take 48,000 IU of vitamin A palmitate daily by mouth from baseline through Month 1 and will continue in the study through Month 2. The screening visit must occur between 60 days and one day prior to the baseline visit while Months 1, 2 and 3 visits must be conducted within a window of ± 14 days from the target day. The tests scheduled at each visit may be split and completed within seven days (including the 7th day) from the visit date. At each visit, the participant will undergo a review of systems, such as an assessment of headache frequency and

severity, as well as an assessment of safety variables. A complete ophthalmologic examination will be performed at each visit to measure outcome variables. If participants in either cohort cannot tolerate the prescribed dose of vitamin A palmitate, they will be instructed to stop taking the supplement and they will be removed from the study.

3.2 Study Objective

The objective of the study is to investigate the potential efficacy and safety of vitamin A palmitate dosing in improving dark adaptation in participants with AMD and abnormal dark adaptation.

3.3 Study Population

Five participants with AMD who met the eligibility criteria were enrolled into Cohort 1. Enrollment for Cohort 1 was halted on May 24, 2019 to focus on enrollment for Cohort 2. Up to five participants with AMD who meet the eligibility criteria may be enrolled in Cohort 2. Up to five additional participants may be accrued in the Cohort 2 to account for participants who withdraw from the study prior to receiving one month of study supplementation for a reason unrelated to an adverse reaction. Participants in Cohort 1 may enroll into Cohort 2 as long as their last intake of vitamin A palmitate was greater than two months prior to their enrollment into Cohort 2.

3.3.1 Participant Eligibility Criteria

3.3.1.1 Inclusion Criteria

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

1. Participant must be 50 years of age or older.
2. Participant must understand and sign the protocol's informed consent document.
3. Any participant of childbearing potential must be willing to undergo urine pregnancy tests throughout the study.
4. Any participant of childbearing potential and any 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 at least one acceptable method of contraception throughout the course of the study and for one week after study supplement discontinuation. 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 (tubal ligation).

5. Participants must agree to notify the study investigator or coordinator if any of their doctors initiate a new prescription medication during the course of this study.
6. Participant must agree to not take ≧8,000 IU vitamin A palmitate outside the study supplementation.
7. For supplementation eligibility, participant must have normal liver function as demonstrated by the Chemistry 20 panel or have mild abnormalities not above grade 1 as defined by the Common Terminology Criteria for Adverse Events v4.0 (CTCAE).
8. Participant must not be pregnant or breast-feeding and must have a negative urine pregnancy test within 24 hours prior to initiation of study medication.

3.3.1.2 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 study therapy.
2. Participant is unable to comply with study procedures or follow-up visits.
3. Participant is already taking vitamin A palmitate supplements ≥ 8,000 IU.
4. Participant has a history of vitamin A deficiency.
5. 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).
6. Participant has a history of hepatitis or liver failure.
7. Participant has chronic gastrointestinal disease.
8. Participant will be excluded if the participant has serologic evidence of an active hepatitis infection.
9. Participant was in Cohort 1 and took his/her last dose of vitamin A palmitate less than two months prior to enrolling in Cohort 2.

3.3.2 Study Eye Eligibility Criteria

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

3.3.2.1 Study Eye Inclusion Criteria

1. The eye must have a best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity score better than or equal to 20/80 (i.e., equal to or better than 54 letters).
2. Participant must have at least one large druse.
3. Abnormal dark adaptation, which is defined as having an AdaptDx test with a RIT of 16 minutes or more at the screening visit. This is at least one standard deviation greater than the average normal RIT and includes room to account for variability in testing. If at any point during current testing or under a previous NEI protocol, a participant has exceeded the 40 minute test ceiling, they will have satisfied the inclusion criteria.

3.3.2.2 Study Eye Exclusion Criteria

1. Presence of advanced macular degeneration with central geographic atrophy or choroidal neovascularization.
2. Presence of definite reticular pseudodrusen.
3. An ocular condition is present (other than AMD) that, in the opinion of the investigator, might 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.).
4. 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).
5. History of major ocular surgery (e.g. cataract extraction, scleral buckle, any intraocular surgery, etc.) within three months prior to study entry.
6. History of Yttrium-Aluminum Garnet (YAG) capsulotomy performed within two months prior to study entry.

3.3.2.3 Choice of Study Eye in Case of Bilateral Disease

If both eyes meet the study eye eligibility criteria described above, the following criteria will be used to select the study eye for the purposes of this investigation:

1. The eye with the better visual acuity will be chosen.
2. If both eyes have equal acuity, the right eye will be arbitrarily chosen as the study eye.

3.4 Outcomes

3.4.1 Primary Study Outcome

The primary outcome for the first cohort is the measurement of dark adaptation parameters (thresholds and kinetics) in the study eye by the following:

- Dark adaptation times and kinetic parameters (i.e., curve parameters) as measured by the AdaptDx comparing baseline and two months after vitamin A palmitate supplementation.
- Dark adaptation parameters (kinetic/curve parameters and pre-bleach thresholds) as measured by the Medmont comparing baseline and two months after vitamin A palmitate supplementation.

The primary outcome for the second cohort is the measurement of dark adaptation parameters (thresholds and kinetics) in the study eye by the following:

- Dark adaptation times and kinetic parameters (i.e., curve parameters) as measured by the AdaptDx comparing baseline and one month after vitamin A palmitate supplementation.
- Dark adaptation parameters (kinetic/curve parameters and pre-bleach thresholds) as measured by the Medmont comparing baseline and one month after vitamin A palmitate supplementation.

3.4.2 Secondary Study Outcomes

The secondary outcomes for both cohorts are changes in low luminance visual acuity (LLVA) and patient-reported outcomes as measured by the low luminance questionnaire (LLQ) comparing baseline to the following timepoints:

- Completion of supplementation (Month 2 in Cohort 1 and Month 1 in Cohort 2)
- One month after completing supplementation (Month 3 in Cohort 1 and Month 2 in Cohort 2).

The secondary outcomes for both cohorts also include the measurement of dark adaptation parameters (thresholds and kinetics) by the following:

- Dark adaptation times and kinetic parameters (i.e., curve parameters) as measured by the AdaptDx comparing baseline and post-treatment follow-up visit
- Dark adaptation parameters (kinetic/curve parameters and pre-bleach thresholds) as measured by the Medmont comparing baseline and post-treatment follow-up visit

Safety outcomes include the number and severity of systemic and ocular toxicities, AEs and infections, occurring throughout the study period.

4.0 DEFINITIONS

Treatment completion visit: The visit corresponding to completion of treatment, occurring at Month 2 in Cohort 1 and Month 1 in Cohort 2. The primary outcome is assessed at this visit.

Post-treatment follow-up visit: The final study visit which occurs one month after completion of treatment, corresponding to Month 3 in Cohort 1 and Month 2 in Cohort 2.

5.0 STATISTICAL CONSIDERATIONS

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

5.1 Sample Size

A total of 18 participants, eight in Cohort 1 and up to ten in Cohort 2, may be enrolled in the study to obtain five participants for the primary outcome analysis for each cohort. No formal sample size calculation was conducted, since this pilot study will not attempt to definitively determine the safety or efficacy of this treatment.

5.2 Analysis Populations

The following analysis populations will be considered for this study:

Screened population: Includes all participants screened, regardless of eligibility determination / enrollment status. Participant disposition will be based on this population.

Enrolled population: Includes all participants enrolled in the study, regardless of compliance, follow-up, or treatment received. Demographic characteristics and compliance will be based on this population. Screen failures are not included in the enrolled population.

Primary analysis population: Includes all enrolled participants who receive investigational product (IP) through the treatment completion visit. The primary, secondary, and exploratory outcome analyses will be based on this population.

Safety population: Includes all enrolled participants who receive at least one dose of IP. All safety analyses will be based on this population.

5.3 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.

5.4 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.

5.5 Handling of Missing Values

In general, missing observations will be excluded from analyses. If a participant receives standard-of-care treatment for neovascular AMD in the study eye during the course of the study, the participant will be withdrawn from the study and the last observation will be carried forward for data analyses. This would be identified manually by reviewing the AEs and natural progression of disease events because it is not included as a termination reason in the case report form.

5.6 Statistical Tests and Adjustment for Multiplicity

Results of statistical analyses are considered significant if the p-value from the statistical test is < 0.05 for two-sided tests and < 0.025 for one-sided tests.

Since all analyses in this study are considered exploratory, no adjustments for multiple comparisons will be made.

5.7 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 SAS version 9.4 or higher, or R v3.6.1 or higher.

6.0 PARTICIPANT DISPOSITION

Overall participant disposition including the number of participants screened, failed screening, enrolled, received at least one dose of IP, received IP through treatment completion visit, discontinued IP early, terminated early from the study and completed study will be summarized by cohort and overall. Reasons for early treatment and study discontinuation will also be summarized (Table 1). This table will be based on the screened population. A consort diagram showing participant flow will also be included as shown in Figure 1.

7.0 PARTICIPANT CHARACTERISTICS

These presentations will be based on the enrolled population.

7.1 Participant Demographics

Demographic data including baseline age, gender, race and ethnicity will be summarized by cohort and overall as in Table 2 and presented by participant. The listing will also include study registration date and indicate the eye determined to be the study eye.

7.2 Medical, Medication, Smoking and Ocular History

Medical, medication and smoking history and history of ophthalmic procedures will be summarized by cohort and overall (Tables 3 and 4, respectively) and presented by participant.

8.0 PARTICIPANT COMPLIANCE

These presentations will be based on the enrolled population.

8.1 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 by cohort and overall.

Effective July 1, 2019, with the implementation of National Institutes of Health (NIH) Intramural Research Program Policy 801, protocol deviations and unanticipated problems are classified by the Investigator as major or minor at the time of data entry (as opposed to serious or not serious), and seriousness of major deviations and unanticipated problems is determined after review by the NIH Institutional Review Board (IRB). The number of events per participant and the type (minor, serious, not serious, or pending determination by IRB) and outcome of events will also be summarized (Table 5). Listings of participant-specific and non-participant-specific protocol deviations and unanticipated problems will be presented.

8.1.1 IP Compliance Deviations

The number of expected doses, number of doses taken, number of doses missed, and the compliance rate will be summarized by participant, cohort, and overall as in Table 6.

For cohort 1, each dose consists of two pills of 8,000 IU of vitamin A palmitate, taken once per day, for a total of 16,000 IU per day. For cohort 2, each dose consists of three pills of 8,000 IU of vitamin A palmitate, taken twice per day, for a total of 48,000 IU per day.

For each participant, the number of expected doses will be calculated as follows:

$$N_{\text{doses expected}} = (\text{Date}_{\text{Month x/ early IP withdrawal}} - \text{Date}_{\text{IP first taken}}) * \text{Number of doses per day}$$

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

$$N_{\text{doses expected}} = (\text{Date}_{\text{Month x/ early IP withdrawal}} - \text{Date}_{\text{IP first taken}} + 1) * \text{Number of doses per day}$$

Where: Month x = Month 2 for Cohort 1 and Month 1 for Cohort 2

$\text{Date}_{\text{IP first taken}}$ = date of the visit when IP was first dispensed to the participant

Number of doses per day = 1 for Cohort 1 and 2 for Cohort 2

The number of pills returned at each study visit will be recorded by the site. Number of doses taken and missed will be calculated for each period timeframe as follows:

$$N_{\text{doses taken}} = (N_{\text{pills dispensed}} - N_{\text{pills returned}}) \text{ / Number of pills per dose}$$

$$N_{\text{doses missed}} = N_{\text{doses expected}} - N_{\text{doses taken}}$$

Where: Number of pills per dose = 2 for Cohort 1 and 3 for Cohort 2.

Compliance rate will be calculated as follows:

$$\text{Compliance Rate} = (N_{\text{doses taken}} / N_{\text{doses expected}}) * 100$$

Participants are considered to have complied with the protocol if they consumed at least 80% of the total expected doses of vitamin A palmitate. Compliance rates falling below 80% will be highlighted in yellow in Table 6.

8.1.2 Study Procedure Deviations

Table 7 will present the expected number of procedures and number and percentage of procedures missed by participant, cohort, procedure, and cumulatively across all participants. Number of procedures missed is defined when the site reports a missed procedure or when the protocol monitors note missed procedures at the site and will be presented as a sum. Expected number of procedures is defined based on the study flowsheet and will also be presented as a sum. Percentage of procedures missed will be calculated as follows:

$$\%_{\text{procedures missed}} = (N_{\text{procedures missed}} / N_{\text{expected procedures}}) * 100$$

8.1.3 Visit Schedule Deviations

The number of expected visits, number and percentage of missed visits, and number and percentage of out of window visits will be summarized by participant, cohort and cumulatively across all participants as in Table 8. Number of expected, missed and out of window visits will be presented as sums. The percentage of missed and out of window study visits will be calculated as follows:

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

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

8.2 Premature Treatment and Study Withdrawals

Participants who withdrew from treatment and study early will be summarized as outlined in Section 6.0 and listed separately along with reason(s) for withdrawal.

9.0 PRIMARY OUTCOMES ANALYSIS

The analysis of primary outcome will be considered exploratory; no adjustment for multiplicity will be performed. These analyses will be based on the primary analysis population.

9.1 Dark Adaptation Times

Change in RIT, as measured by the AdaptDx, from baseline in the study eye at treatment completion visit will be summarized (Table 9) and listed (Listing 1) for each cohort.

For each cohort, the mean change in RIT in the study eye at the treatment completion visit from baseline will be assessed using a Student's paired t-test (TTEST procedure in SAS) (Table 9). The following hypothesis will be tested at a type I error rate of 5%, where $\mu_{\text{Baseline RIT}}$ is the mean RIT at baseline and $\mu_{\text{treatment completion RIT}}$ is the mean RIT at at the treatment completion visit:

$$H_o: \mu_{\text{Baseline RIT}} = \mu_{\text{treatment completion RIT}}$$

$$H_A: \mu_{\text{Baseline RIT}} \neq \mu_{\text{treatment completion RIT}}$$

9.2 Dark Adaptation Parameters

Changes in AdaptDx curve parameters measured at baseline and at treatment completion will be assessed by first fitting a two part (exponential and linear) curve to the data:

$$y = ae^{-bx} + c \max(x\text{-}d, 0) + e,$$

where y is the threshold, b is the cone adaptation rate, x is time after cessation of bleach, c is the rod slope, d is the time of the rod cone break, and $a + e$ is the cone-rod plateau. Changes in pre-bleach thresholds and kinetic parameters as measured by the Medmont in the study eye at the treatment completion visit will be compared to baseline for each cohort, as described in Flynn et. al.[18] All dark adaptation parameters will be analyzed by researchers at the NEI.

10.0 SECONDARY OUTCOMES ANALYSIS

The analysis of secondary outcomes will be considered exploratory; no adjustment for multiplicity will be performed. Secondary analyses will be based on the primary analysis population.

10.1 Low Luminance Visual Acuity (LLVA)

Change from baseline in LLVA total letters read in the study eye at the treatment completion visit and the post-treatment follow-up visit will be summarized and presented by participant for each cohort (Table 10, Listing 2).

10.2 Low Luminance Questionnaire (LLQ)

The LLQ is used to assess self-reported visual problems under low luminance and at night. The 32-item LLQ has six subscales: driving, extreme lighting, mobility, emotional distress, general dim lighting and peripheral vision. Each subscale score is derived by taking the average of a subset of questions from the LLQ, and a composite score is calculated as a weighted average of the subscales.[19]

Change from baseline in LLQ subscale and composite scores at the treatment completion visit and post-treatment follow-up visit will be summarized and presented by participant for each cohort (Table 11, Listing 3).

10.3 Dark Adaptation Times

A similar analysis to the primary outcome analysis for dark adaptation times described in Section 9.1 will be conducted comparing baseline to post-treatment follow-up visit in each cohort (Table 9, Listing 1).

10.4 Dark Adaptation Parameters

A similar analysis to the primary outcome analysis for dark adaptation parameters described in Section 9.2 will be conducted comparing baseline to post-treatment follow-up visit in each cohort. All dark adaptation parameters will be analyzed by researchers at the NEI.

11.0 EXPLORATORY ANALYSES

11.1 Dark Adaptation Times

To explore the effect of within-subject correlation, a mixed effects model (Model 1) will be fit using PROC MIXED in SAS to assess mean change from baseline in RIT in the study eye at the treatment completion visit and post-treatment follow-up visit in Cohort 1.

$$\text{Model 1: } \hat{Y}_{ij} = \hat{\beta}_o + \hat{\beta}_1 * \text{Time}_j + b_i + \varepsilon_t$$

Where:

$\hat{Y}_{ij}$ = Estimate of mean RIT for participant i at timepoint j

$\hat{\beta}_o$ = Estimate of mean RIT at baseline

$\hat{\beta}_1$ = Estimate of mean rate of change (monthly) in RIT

Time_j = Time in months from baseline

b_i = Random effect for baseline RIT in the i^{th} participant

ε_t = Random variability not explained by the model, which is assumed to be normally distributed and independent across participants and time

Based on this model, the estimated mean difference in RIT between baseline and Month 2 is $2\beta_1$, and the estimated mean difference between baseline and Month 3 is $3\beta_1$. The following hypothesis will be tested at a type I error rate of 5%:

$$H_o: \beta_1 = 0$$

$$H_A: \beta_1 \neq 0$$

The results of this analysis will be summarized as in Table 9.

11.2 Low Luminance Visual Acuity (LLVA)

For each cohort, change from baseline in LLVA total letters read at the treatment completion visit and post-treatment follow-up visit will be assessed using Student's paired t-test similar to the analysis of primary outcome as outlined in Section 9.1 for the study eye. Additionally, a model similar to Model 1 will be fitted to assess the mean difference in total letters read in the study eye

at the treatment completion visit and post-treatment follow-up visit compared to baseline in Cohort 1 (Table 10).

11.3 Low Luminance Questionnaire (LLQ)

For each cohort, change from baseline at the treatment completion visit and post-treatment follow-up visit for each subscale and the composite score will be assessed using Student's paired t-test similar to the analysis of the primary outcome as outlined in Section 9.1. Additionally, a model similar to Model 1 will be fitted to assess the mean difference in the composite score at the treatment completion visit and post-treatment follow-up visit compared to baseline in Cohort 1 (Table 11).

12.0 SAFETY OUTCOMES

These presentations will be based on the safety population. All relevant information will be listed.

12.1 Adverse Events (AEs)

AEs reported throughout the study period will be presented in a listing with details including date reported, description, severity, relatedness to IP, outcome and date resolved. Total number and percentage of participants with AEs will be summarized by cohort and overall and categorized by severity of the AE, ocular specification (ocular vs. systemic), outcome, and relation to IP (Table 12).

AEs will also be summarized by system organ class (SOC) and preferred term (PT) (Table 13). If sufficient data are present, summaries similar to Table 12 and Table 13 will be generated for all serious adverse events (SAEs).

13.0 OTHER SAFETY OUTCOMES

These presentations will be based on the safety population. All relevant information will be listed.

13.1 Natural Progressions of the Disease

Events corresponding to natural progression of the disease will be listed by participant. If sufficient data are present, summaries similar to Tables 12 and 13 will be presented for these events.

13.2 Laboratory Assessments

Hepatitis screening is performed at the screening visit. Serum vitamin A levels and hepatic panels are performed at the screening visit and all follow-up visits. Abnormal results from laboratory assessments performed at screening are reported at the baseline visit.

Frequency and percentage of participants reporting laboratory abnormalities at baseline and shift from baseline at each follow-up visit will be summarized by cohort and overall as in Table 14.

14.0 OTHER OPHTHALMIC ASSESSMENTS

These presentations will be based on the safety population. All relevant information will be listed. Outcome measurements or relative change in outcome measurements may be plotted against time.

14.1 Rod-Intercept Time (RIT)

RIT, as measured by the AdaptDx™, is assessed at baseline and all follow-up visits in the study eye. RIT at all visits and change from baseline at all follow-up visits will be presented by participant and summarized by cohort and overall as in Table 15.

14.2 Best-Corrected Visual Acuity (BCVA)

Visual acuity is assessed at baseline and all follow-up visits in both eyes. BCVA with manifest refraction is scheduled to be performed at baseline and Month 2 and if a change in BCVA total letters read of ≥ 10 (≥ 0.20 logMAR) since previous visit is observed. 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.

Total letters read at each visit and change from baseline at each follow-up visit will be presented by participant for both eyes and summarized by cohort and overall as in Table 16. Participants experiencing loss of ≥ 15 letters from baseline may be withdrawn from the study at investigator's discretion. Frequency and percentage of participants presenting with a loss of ≥ 15 letters from baseline at each follow-up visit will be included in Table 16.

14.3 Low Luminance Visual Acuity (LLVA)

LLVA total letters read is assessed at baseline and all follow-up visits in both eyes. Total letters read at each visit and change from baseline at each follow-up visit will be presented by participant and summarized by cohort and overall as in Table 17.

14.4 Low Luminance Questionnaire (LLQ)

The low luminance questionnaire is completed at baseline and all follow-up visits. Subscale and composite scores at baseline and change from baseline at each follow-up visit will be presented by participant and summarized by cohort and overall (Table 18).

14.5 Intraocular Pressure (IOP)

IOP is assessed at baseline and all follow-up visits in both eyes. IOP measurements at each visit and change from baseline at each follow-up visit will be presented by participant and summarized for each eye by cohort and overall as in Table 19.

14.6 Optic Nerve Papilledema, Headache, and Medication Assessment

Participants are assessed at each visit for headache and presence of optic nerve papilledema. Additionally, vitamin A palmitate consumption outside of the study is assessed at each follow-up visit. Number and percentage of participants experiencing optic nerve papilledema in each eye, headache classified by severity, and vitamin A palmitate consumption outside of the study will be summarized by cohort and overall as in Table 20; relevant information will be listed by participant.

14.7 Other Ophthalmic Assessments

The following additional ophthalmic assessments are conducted at each visit and will be presented by participant. Number and percentage of participants experiencing these events will be summarized as in Table 21.

- Presence and size of drusen
- Presence of hypo/hyperpigmentation
- Presence of RPE detachment
- Choroidal neovascularization
- Subretinal / Intraretinal fluid
- Geographic atrophy
- Lens aphakia

- Pseudophakic lens
- Nuclear cataract score
- Posterior Subcapsular Cataract (PSC) cataract score
- Presence of RPD (at Baseline)

15.0 RATIONALE FOR ANY DEVIATION FROM PRE-SPECIFIED ANALYSIS PLAN

Depending on the nature of the data, certain outcomes may be presented differently than outlined in this analysis pan. Tables and figures will be presented only when an adequate amount of data are available. Data for some outcomes may not be available to the CC at every visit. Because of this, these outcomes may not be presented until after study closure.

16.0 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 CC.

17.0 REFERENCES

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18.0 MOCK SHELLS

TABLES

Table 1. Participant Disposition

Disposition	Cohort 1 N (%)[a]	Cohort 2 N (%)[a]	Overall N (%)[a]
Screened	**x**	**x**	**x**
Screen failure[b]	x (x)	x (x)	x (x)
Enrolled[b]	**x (x)**	**x (x)**	**x (x)**
Received at least one dose of IP	x (x)	x (x)	x (x)
Discontinued IP Early	**x (x)**	**x (x)**	**x (x)**
Reason for Discontinuation[c]			
Participant non-compliance	x (x)	x (x)	x (x)
Therapy unavailable	x (x)	x (x)	x (x)
Safety withdrawal	x (x)	x (x)	x (x)
Lack of efficacy	x (x)	x (x)	x (x)
Other	x (x)	x (x)	x (x)
Terminated Early from the Study	**x (x)**	**x (x)**	**x (x)**
Reason for Termination[d]			
AE/intercurrent illness	x (x)	x (x)	x (x)
Death	x (x)	x (x)	x (x)
Insufficient therapeutic response	x (x)	x (x)	x (x)
Lost to follow-up	x (x)	x (x)	x (x)
Participant request/refusal	x (x)	x (x)	x (x)
Early study closure	x (x)	x (x)	x (x)
Protocol deviation/violation	x (x)	x (x)	x (x)
Other	x (x)	x (x)	x (x)
Received IP through treatment completion visit[e]	**x (x)**	**x (x)**	**x (x)**
Completed Study	**x (x)**	**x (x)**	**x (x)**

[a] Denominators are the number of participants in the enrolled population in the respective cohort or overall, unless otherwise specified. Percentages are rounded to the nearest whole number.
[b] Denominators are the number of participants in the screened population.
[c] Denominators are the number of participants who discontinued IP early.
[d] Denominators are the number of participants who terminated early from the study.
[e] Treatment completion visit corresponds to Month 2 for Cohort 1 and Month 1 for Cohort 2.

Table 2. Summary of Participant Demographics

Demographic Characteristics	Cohort 1 (N=X)[a]	Cohort 2 (N=X)[a]	Overall (N=X)[a]
Gender, N (%)			
Male	x (x)	x (x)	x (x)
Female	x (x)	x (x)	x (x)
Age Category (years) at Baseline, N (%)			
50-70	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)
86-89	x (x)	x (x)	x (x)
>89	x (x)	x (x)	x (x)
Age (years) at Baseline[b]			
N	x	x	x
Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)
Median	x.x	x.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)
Unknown	x (x)	x (x)	x (x)
Race, N (%)			
American Indian or Alaskan Native	x (x)	x (x)	x (x)
Asian	x (x)	x (x)	x (x)
Black	x (x)	x (x)	x (x)
Hawaiian or Pacific Islander	x (x)	x (x)	x (x)
White	x (x)	x (x)	x (x)
Multiple race	x (x)	x (x)	x (x)
Unknown	x (x)	x (x)	x (x)

[a] Column header counts and denominators are the number of participants in the enrolled population in the respective cohort or overall. Percentages are rounded to the nearest whole number.
[b] Participants over 89 years of age are excluded.

Table 3. Medical, Medication, and Smoking History

Conditions	Cohort 1 (N=X) N (%)[a]	Cohort 2 (N=X) N (%)[a]	Overall (N=X) N (%)[a]
Any Medical Condition	**x (x)**	**x (x)**	**x (x)**
Diabetes			
Yes	x (x)	x (x)	x (x)
No	x (x)	x (x)	x (x)
Vitamin A deficiency			
Yes	x (x)	x (x)	x (x)
No	x (x)	x (x)	x (x)
Hepatitis			
Yes	x (x)	x (x)	x (x)
No	x (x)	x (x)	x (x)
Liver failure			
Yes	x (x)	x (x)	x (x)
No	x (x)	x (x)	x (x)
Cancer			
Yes	x (x)	x (x)	x (x)
No	x (x)	x (x)	x (x)
Chronic gastrointestinal disease			
Yes	x (x)	x (x)	x (x)
No	x (x)	x (x)	x (x)
Migraine / headache			
Yes	x (x)	x (x)	x (x)
No	x (x)	x (x)	x (x)
Medication History			
Currently taking Vitamin A palmitate			
Yes	x (x)	x (x)	x (x)
No	x (x)	x (x)	x (x)
Currently taking anticoagulants / Coumadin[b]			
Yes	x (x)	x (x)	x (x)
No	x (x)	x (x)	x (x)
Smoking History			
Currently smokes			
Yes	x (x)	x (x)	x (x)
No	x (x)	x (x)	x (x)
Ever smoked			
Yes	x (x)	x (x)	x (x)
No	x (x)	x (x)	x (x)

[a] Column header count and denominators are the number of participants in the enrolled population in the respective cohort or overall. Percentages are rounded to the nearest whole number.

[b] Prior to protocol v7.0 (IRB approved February 24, 2022), participants were assessed for prescription of any anticoagulant at enrollment. With protocol v7.0 and above, participants are assessed for prescription of Coumadin at enrollment.

Table 4. Ocular History

	Cohort 1			Cohort 2			Overall		
Procedures	**Study Eye[a] (N=X) N(%)**	**Fellow Eye[a] (N=X) N(%)**	**Total[a,b] (N=X) N(%)**	**Study Eye[a] (N=X) N(%)**	**Fellow Eye[a] (N=X) N(%)**	**Total[a,b] (N=X) N(%)**	**Study Eye[a] (N=X) N(%)**	**Fellow Eye[a] (N=X) N(%)**	**Total[a,b] (N=X) N(%)**
Any Ocular Procedure	**x (x)**	**x (x)**	**x (x)**	**x (x)**	**x (x)**	**x (x)**	**x (x)**	**x (x)**	**x (x)**
Ocular surgery within 3 months									
Yes	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
YAG laser within 2 months									
Yes	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Anti-VEGF injection									
Yes	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Other Procedure									
Yes	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

[a] Column header counts and denominators are the number of participants in the enrolled population in the respective cohort or overall. Percentages are rounded to the nearest whole number.
[b] If a participant reported an ocular procedure in both eyes, the participant will be counted only once in this column.

Table 5. Protocol Deviations and Unanticipated Problems

	Participant-Specific						Non-Participant Specific	Total
	Number of Events			Number of Participants with Events N (%)[a]			Number of Events	Number of Events
	Cohort 1	Cohort 2	Overall	Cohort 1 (N=X)	Cohort 2 (N=X)	Overall (N=X)		
All events[b]	**x**	**x**	**x**	**x (x)**	**x (x)**	**x (x)**	**x**	**x**
Protocol deviations	x	x	x	x (x)	x (x)	x (x)	x	x
Unanticipated problems	x	x	x	x (x)	x (x)	x (x)	x	x
Type[c]								
Minor	x	x	x	x (x)	x (x)	x (x)	x	x
Not serious	x	x	x	x (x)	x (x)	x (x)	x	x
Serious	x	x	x	x (x)	x (x)	x (x)	x	x
Determination Pending	x	x	x	x (x)	x (x)	x (x)	x	x
Outcome								
Participant follow-up continues	x	x	x	x (x)	x (x)	x (x)	x	x
Participant follow-up terminated	x	x	x	x (x)	x (x)	x (x)	x	x
Investigational product remains stable	x	x	x	x (x)	x (x)	x (x)	x	x
Investigational product returned or discarded	x	x	x	x (x)	x (x)	x (x)	x	x
Other	x	x	x	x (x)	x (x)	x (x)	x	x

[a] Column header count and denominators are the total number of participants enrolled in the respective cohort or overall. Percentages are rounded to the nearest whole number.

[b] Events that are both protocol deviations and unanticipated problems are included in both rows.

[c] Prior to July 1, 2019, Investigators classified deviations and unanticipated problems as serious or not serious.Effective July 1, 2019, Investigators classify deviations and unanticipated problems as minor or major and IRB classifies the major deviations and unanticipated problems as serious or not serious. Determination pending category corresponds to those major deviations or unanticipated problems that the IRB is yet to classify as serious or not serious.

Table 6. IP Compliance

Cohort	Participant ID	Expected Number of Doses Taken	Number of Doses Taken	Number of Doses Missed[a]	Compliance Rate (%)[b]
1	NEI001	x	x	x	xx.x
	NEI002	x	x	x	xx.x
	…	x	x	x	xx.x
	Cohort 1 Total	**x**	**x**	**x**	**xx.x**
2	NEI101	x	x	x	xx.x
	…	x	x	x	xx.x
	Cohort 2 Total	**x**	**x**	**x**	**xx.x**
Overall	**Total**	**x**	**x**	**x**	**xx.x**

[a] Negative numbers indicate the participant took more than the expected number of doses.
[b] Compliance rates falling below the protocol-defined threshold of 80% are highlighted in yellow. Percentages are rounded to the nearest tenth.

Table 7. Study Procedure Deviations

	Number of Expected Procedures[a]	Number of Missed Procedures[b]	Percentage (%) of Missed Procedures[c]
By participant			
Cohort 1			
NEI001	x	x	xx.x
NEI002	x	x	xx.x
…	x	x	xx.x
Total	**x**	**x**	**xx.x**
Cohort 2			
NEI101	x	x	xx.x
NEI102	x	x	xx.x
…	x	x	xx.x
Total	**x**	**x**	**xx.x**
By procedure			
AdaptDx Dark Adaptation Testing	x	x	xx.x
Adverse Event Assessment	x	x	xx.x
…	x	x	xx.x
Overall Total	**x**	**x**	**xx.x**

[a] The number of expected procedures is defined based on the study flowsheet included in the protocol.
[b] Missed procedures are defined when the site reports a missed procedure or when the protocol monitors note missed procedures at a site visit.
[c] Percentages are rounded to the nearest tenth.

Table 8. Missed and Out of Window Follow-Up Study Visits

Cohort	Participant ID	Number of Expected Visits	Number of Missed Visits	Percentage of Missed Visits[a]	Number of Out of Window Visits	Percentage of Out of Window Visits[a]	Visits Missed or Out of Window
1	NEI001	x	x	xx.x	x	xx.x	xxx, xxx
	NEI002	x	x	xx.x	x	xx.x	xxx, xxx
	…	x	x	xx.x	x	xx.x	xxx, xxx
	Cohort 1 Total	**x**	**x**	**xx.x**	**x**	**xx.x**	
2	NEI101	x	x	xx.x	x	xx.x	xxx, xxx
	…	x	x	xx.x	x	xx.x	xxx, xxx
	Cohort 2 Total	**x**	**x**	**xx.x**	**x**	**xx.x**	
Overall	**Total**	**x**	**x**	xx.x	**x**	**xx.x**	

[a] Percentages are rounded to the nearest tenth.

Table 9. Analysis of Primary Outcome of Change in Dark Adaptation Rod Intercept Time (RIT) from Baseline in the Study Eye and Corresponding Secondary and Exploratory Analyses

	Cohort 1							Cohort 2			
	Rod Intercept Time (Minutes)		Paired T-Test[a]		Mixed-Effects Model[b]			Rod Intercept Time (Minutes)		Paired T-Test[a]	
Visit[c]	Value	Δ[d]	Mean (95% CI)	p-value	β_1	SE (β_1)	p-value	Value	Δ[d]	Mean (95% CI)	p-value
Baseline											
N	x							x			
Mean (SD)	x.xx (x.xxx)							x.xx (x.xxx)			
Median	x.xx							x.xx			
Range (min, max)	(x.x, x.x)							(x.x, x.x)			
Treatment Completion											
N	x	x						x	x		
Mean (SD)	x.xx (x.xxx)	x.xx (x.xxx)						x.xx (x.xxx)	x.xx (x.xxx)		
Median	x.xx	x.xx						x.xx	x.xx		
Range (min, max)	(x.x, x.x)	(x.x, x.x)						(x.x, x.x)	(x.x, x.x)		
Statistical Test			x.xx (x.xx, x.xx)	x.xxx	x.xx	x.xxx	x.xxx			x.xx (x.xx, x.xx)	x.xxx
Post-treatment Follow-up											
N	x	x						x	x		
Mean (SD)	x.xx (x.xxx)	x.xx (x.xxx)						x.xx (x.xxx)	x.xx (x.xxx)		
Median	x.xx	x.xx						x.xx	x.xx		
Range (min,max)	(x.x, x.x)	(x.x, x.x)						(x.x, x.x)	(x.x, x.x)		
Statistical Test			x.xx (x.xx, x.xx)	x.xxx	x.xx	x.xxx	x.xxx			x.xx (x.xx, x.xx)	x.xxx

Cells highlighted in green correspond to the primary outcome analysis; cells highlighted in yellow correspond to secondary analyses and the remaining analyses correspond to exploratory analyses.

[a] Paired t-test comparing RIT at treatment completion visit or post-treatment follow-up visit vs. baseline at two-sided type 1 error rate of 5%.

[b] Mixed-effects longitudinal model conducted at two-sided type 1 error rate of 5%. The coefficient β_1 corresponds to the estimate of the mean rate of change(monthly) in DA RIT. [COV] covariance structure provided the best model fit.

[c] Treatment completion visit corresponds to Month 2 in Cohort 1, and Month 1 in Cohort 2. Post-treatment follow-up visit corresponds to Month 3 in Cohort 1, and Month 2 in Cohort 2.

[d] Δ implies change from baseline.

Programming note: Replace [COV] with actual covariance structure that provided the best model fit.

Table 10. Analysis of Secondary Outcome of Change in LLVA Total Letters Read from Baseline in the Study Eye and Corresponding Exploratory Analyses

	Cohort 1							Cohort 2			
	Total Letters Read		Paired T-Test[a]		Mixed-Effects Model[b]			Total Letters Read		Paired T-Test[a]	
Visit[c]	Value	Δ[d]	Mean (95% CI)	p-value	β_1	SE (β_1)	p-value	Value	Δ[d]	Mean (95% CI)	p-value
Baseline											
N	x							x			
Mean (SD)	x.x (x.xx)							x.x (x.xx)			
Median	x.x							x.x			
Range (min, max)	(x, x)							(x, x)			
Treatment Completion											
N	x	x						x	x		
Mean (SD)	x.x (x.xx)	x.x (x.xx)						x.x (x.xx)	x.x (x.xx)		
Median	x.x	x.x						x.x	x.x		
Range (min, max)	(x, x)	(x, x)						(x, x)	(x, x)		
Statistical Test			x.xx (x.xx, x.xx)	x.xxx	x.xx	x.xxx	x.xxx			x.xx (x.xx, x.xx)	x.xxx
Post-treatment Follow-up											
N	x	x						x	x		
Mean (SD)	x.x (x.xx)	x.x (x.xx)						x.x (x.xx)	x.x (x.xx)		
Median	x.x	x.x						x.x	x.x		
Range (min,max)	(x, x)	(x, x)						(x, x)	(x,x)		
Statistical Test			x.xx (x.xx, x.xx)	x.xxx	x.xx	x.xxx	x.xxx			x.xx (x.xx, x.xx)	x.xxx

Cells highlighted in yellow correspond to the secondary outcome analysis, and the remaining analyses correspond to exploratory analyses

[a] Paired t-test comparing LLVA at treatment completion visit or post-treatment follow-up visit vs. baseline at two-sided type 1 error rate of 5%.

[b] Mixed-effects longitudinal model conducted at two-sided type 1 error rate of 5%. The coefficient β_1 corresponds to the estimate of the mean rate of change (monthly) in LLVA total letters read. [COV] covariance structure provided the best model fit.

[c] Treatment completion visit corresponds to Month 2 in Cohort 1, and Month 1 in Cohort 2. Post-treatment follow-up visit corresponds to Month 3 in Cohort 1, and Month 2 in Cohort 2.

[d] Δ implies change from baseline.

.

Programming note: Replace [COV] with actual covariance structure that provided the best model fit.

Table 11. Analysis of Secondary Outcome of Change in LLQ Subscale and Composite Scores from Baseline and Corresponding Exploratory Analyses

	Cohort 1							Cohort 2			
	Score		Paired t-test[a]		Mixed Effects Model[b]			Score		Paired t-test[a]	
Subscale / Visit[c]	Value	Δ[d]	Mean (95% CI)	p-value	β_1	SE (β_1)	p-value	Value	Δ[d]	Mean (95% CI)	p-value
Driving											
Baseline											
N	x							x			
Mean (SD)	x.xx (x.xxx)							x.xx (x.xxx)			
Median	x.xx							x.xx			
Range (min, max)	(x.x, x.x)							(x.x, x.x)			
Treatment Completion											
N	x	x						x	x		
Mean (SD)	x.xx (x.xxx)	x.xx (x.xxx)						x.xx (x.xxx)	x.xx (x.xxx)		
Median	x.xx	x.xx						x.xx	x.xx		
Range (min, max)	(x.x, x.x)	(x.x, x.x)						(x.x, x.x)	(x.x, x.x)		
Statistical Test			x.xx (x.xx, x.xx)	x.xxx						x.xx (x.xx, x.xx)	x.xxx
Post-treatment follow-up											
N	x	x						x	x		
Mean (SD)	x.xx (x.xxx)	x.xx (x.xxx)						x.xx (x.xxx)	x.xx (x.xxx)		
Median	x.xx	x.xx						x.xx	x.xx		
Range (min, max)	(x.x, x.x)	(x.x, x.x)						(x.x, x.x)	(x.x, x.x)		
Statistical Test			x.xx (x.xx, x.xx)	x.xxx						x.xx (x.xx, x.xx)	x.xxx
…											
Composite Score[e]											
Baseline											
…											
Treatment Completion											
N	x	x						x	x		
Mean (SD)	x.xx (x.xxx)	x.xx (x.xxx)						x.xx (x.xxx)	x.xx (x.xxx)		
Median	x.xx	x.xx						x.xx	x.xx		
Range (min, max)	(x.x, x.x)	(x.x, x.x)						(x.x, x.x)	(x.x, x.x)		
Statistical Test			x.xx (x.xx, x.xx)	x.xxx	x.xx	x.xxx	x.xxx			x.xx (x.xx, x.xx)	x.xxx
Post-treatment follow-up											
N	x	x						x	x		
Mean (SD)	x.xx (x.xxx)	x.xx (x.xxx)						x.xx (x.xxx)	x.xx (x.xxx)		
Median	x.xx	x.xx						x.xx	x.xx		
Range (min, max)	(x.x, x.x)	(x.x, x.x)						(x.x, x.x)	(x.x, x.x)		

Table 11. Analysis of Secondary Outcome of Change in LLQ Subscale and Composite Scores from Baseline and Corresponding Exploratory Analyses (continued)

	Cohort 1							Cohort 2			
	Score		Paired t-test[a]		Mixed Effects Model[b]			Score		Paired t-test[a]	
Subscale / Visit[c]	Value	Δ[d]	Mean (95% CI)	p-value	β_1	SE (β_1)	p-value	Value	Δ[d]	Mean (95% CI)	p-value
Statistical Test			x.xx (x.xx, x.xx)	x.xxx	x.xx	x.xxx	x.xxx			x.xx (x.xx, x.xx)	x.xxx

Cells highlighted in yellow correspond to the secondary outcome analysis and the remaining correspond to exploratory analyses.
[a] Paired t-test comparing LLQ subscale and composite scores at treatment completion visit or post-treatment follow-up visit vs. baseline at two-sided type I error rate of 5%.
[b] Mixed-effects longitudinal model conducted at two-sided type 1 error rate of 5%. The coefficient β_1 corresponds to the estimate of the mean rate of change (monthly) in the score. The mixed-effects model was fit for the composite score only. [COV] covariance structure provided the best model fit.
[c] Treatment completion visit corresponds to Month 2 in Cohort 1, and Month 1 in Cohort 2. Post-treatment follow-up visit corresponds to Month 3 in Cohort 1, and Month 2 in Cohort 2.
[d] Δ implies change from baseline.
[e] Composite score is an average of the six weighted subscale scores.

Programming note: Replace [COV] with actual covariance structure that provided the best model fit.

Table 12. Summary of Adverse Events (AEs)

	Participants with Events N (%)[a]			Number of Events N		
	Cohort 1 (N=X)	Cohort 2 (N=X)	Overall (N=X)	Cohort 1	Cohort 2	Overall
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
Ocular Specification						
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 sequelae	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						
Related	x (x)	x (x)	x (x)	x	x	x
Not Related	x (x)	x (x)	x (x)	x	x	x

[a] Column header counts and denominators are the number of participants in the safety population in the respective cohort or overall. Participants may be counted in more than one category. Percentages are rounded to the nearest whole number.

Table 13. AEs by System Organ Class (SOC) and Preferred Term (PT)

MedDRA System Organ Class/ Preferred Term[a,b]	Participants with Events N (%)[c]			Number of Events N		
	Cohort 1 (N=X)	Cohort 2 (N=X)	Overall (N=X)	Cohort 1	Cohort 2	Overall
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
…	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
…	x (x)	x (x)	x (x)	x	x	x
…	x (x)	x (x)	x (x)	x	x	x

[a] MedDRA version XX.X.

[b] System organ classes (SOCs) are presented in descending order of number of events reported; preferred terms (PTs) within each SOC are also presented in descending order of number of events reported.

[c] Column header counts and denominators are the number of participants in the safety population in the respective cohort or overall. Percentages are rounded to the nearest whole number. Participants are counted at most once in each row. Therefore, a participant may experience events corresponding to multiple PTs within an SOC, but the sum of participants in the PT rows may not add up to the corresponding SOC row.

Table 14. Summary of Laboratory Assessments Over Time

	Abnormal Findings[a] n/N (%)			Any Change from Baseline n/N (%)			Clinically Significant Change from Baseline n/N (%)		
Visit	**Cohort 1**	**Cohort 2**	**Overall**	**Cohort 1**	**Cohort 2**	**Overall**	**Cohort 1**	**Cohort 2**	**Overall**
Baseline	x/x (x)	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)
Month 2				x/x (x)	x/x (x)	x/x (x)	x/x (x)	x/x (x)	x/x (x)
Month 3[b]				x/x (x)			x/x (x)		

Denominators are the number of participants in the safety population who completed the specified visit, in the respective cohort or overall. Percentages are rounded to the nearest whole number.

[a] Abnormal results from screening are reported at baseline.

[b] Only participants in Cohort 1 complete Month 3.

Table 15. Summary of Dark Adaptation Rod Intercept Time

	Rod Intercept Time (minutes)			Change from Baseline		
Visit	**Cohort 1**	**Cohort 2**	**Overall**	**Cohort 1**	**Cohort 2**	**Overall**
Baseline						
N	x	x	x			
Mean (SD)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)			
Median	x.xx	x.xx	x.xx			
Range (min, max)	(x.x, x.x)	(x.x, x.x)	(x.x, x.x)			
Month 1						
N	x	x	x	x	x	x
Mean (SD)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)
Median	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
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)
Month 2						
N	x	x	x	x	x	x
Mean (SD)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)
Median	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
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)
Month 3[a]						
N	x			x		
Mean (SD)	x.xx (x.xxx)			x.xx (x.xxx)		
Median	x.xx			x.xx		
Range (min, max)	(x.x, x.x)			(x.x, x.x)		

[a] Only participants in Cohort 1 complete Month 3.

Table 16. Summary of BCVA Total Letters Read

	BCVA Total Letters Read						Change from Baseline					
	Cohort 1		Cohort 2		Overall		Cohort 1		Cohort 2		Overall	
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						
Mean (SD)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x (x)	x (x)						
Median	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)						
Month 1												
N	x	x	x	x	x	x	x	x	x	x	x	x
Mean (SD)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)
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
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)
≥ 15 letter loss, N (%)[a]	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												
N	x	x	x	x	x	x	x	x	x	x	x	x
Mean (SD)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)
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
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)
≥ 15 letter loss, N (%)[a]	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 3[b]												
N	x	x					x	x				
Mean (SD)	x.x (x.xx)	x.x (x.xx)					x.x (x.xx)	x.x (x.xx)				
Median	x.x	x.x					x.x	x.x				
Range (min, max)	(x, x)	(x, x)					(x, x)	(x, x)				
≥ 15 letter loss, N (%)[a]	x (x)	x (x)					x (x)	x (x)				

[a] Denominators are the number of participants in the safety population with a non-missing value for the specified visit, in the respective cohort or overall.
[b] Only participants in Cohort 1 complete Month 3.

Table 17. Summary of LLVA Total Letters Read

	LLVA Total Letters Read						Change from Baseline					
	Cohort 1		Cohort 2		Overall		Cohort 1		Cohort 2		Overall	
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						
Mean (SD)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)						
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)						
Month 1												
N	x	x	x	x	x	x	x	x	x	x	x	x
Mean (SD)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)
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
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)
Month 2												
N	x	x	x	x	x	x	x	x	x	x	x	x
Mean (SD)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)
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
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)
Month 3[a]												
N	x	x					x	x				
Mean (SD)	x.x (x.xx)	x.x (x.xx)					x.x (x.xx)	x.x (x.xx)				
Median	x.x	x.x					x.x	x.x				
Range (min, max)	(x, x)	(x, x)					(x, x)	(x, x)				

[a] Only participants in Cohort 1 complete Month 3.

Table 18. Summary of LLQ Subscale and Composite Scores

	Score			Change from Baseline		
Subscale / Visit	**Cohort 1**	**Cohort 2**	**Overall**	**Cohort 1**	**Cohort 2**	**Overall**
Driving						
Baseline						
N	x	x	x			
Mean (SD)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)			
Median	x.xx	x.xx	x.xx			
Range (min, max)	(x.x, x.x)	(x.x, x.x)	(x.x, x.x)			
Month 1						
N	x	x	x	x	x	x
Mean (SD)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)
Median	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
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)
Month 2						
N	x	x	x	x	x	x
Mean (SD)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)
Median	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
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)
Month 3[a]						
N	x			x		
Mean (SD)	x.xx (x.xxx)			x.xx (x.xxx)		
Median	x.xx			x.xx		
Range (min, max)	(x.x, x.x)			(x.x, x.x)		
Extreme lighting						
Baseline						
N	x	x	x			
Mean (SD)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)			
Median	x.xx	x.xx	x.xx			
Range (min, max)	(x.x, x.x)	(x.x, x.x)	(x.x, x.x)			
…						
Composite Score[b]						
…						

[a] Only participants in Cohort 1 complete Month 3.
[b] Composite score is an average of the six weighted subscale scores.

Table 19. Summary of IOP

	IOP (mmHg)						Change from Baseline					
	Cohort 1		Cohort 2		Overall		Cohort 1		Cohort 2		Overall	
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						
Mean (SD)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)						
Median	x.x	x.x	x.x	x.x	x.x	x.xx						
Range (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
Mean (SD)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)
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
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)
Month 2												
N	x	x	x	x	x	x	x	x	x	x	x	x
Mean (SD)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)
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
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)
Month 3[a]												
N	x	x					x	x				
Mean (SD)	x.x (x.xx)	x.x (x.xx)					x.x (x.xx)	x.x (x.xx)				
Median	x.x	x.x					x.x	x.x				
Range (min, max)	(x, x)	(x, x)					(x, x)	(x, x)				

[a] Only participants in Cohort 1 complete Month 3.

Table 20. Summary of Optic Nerve Papilledema, Headache, and Medication Assessment

	Participants with Event N (%)[a]		
Visit / Assessment	**Cohort 1**	**Cohort 2**	**Overall**
Baseline			
Optic Nerve Papilledema			
Study Eye			
Yes	x (x)	x (x)	x (x)
No	x (x)	x (x)	x (x)
Fellow Eye			
Yes	x (x)	x (x)	x (x)
No	x (x)	x (x)	x (x)
Headache			
None	x (x)	x (x)	x (x)
Mild	x (x)	x (x)	x (x)
Moderate	x (x)	x (x)	x (x)
Severe	x (x)	x (x)	x (x)
Month 1			
Optic Nerve Papilledema			
Study Eye			
Yes	x (x)	x (x)	x (x)
No	x (x)	x (x)	x (x)
Fellow Eye			
Yes	x (x)	x (x)	x (x)
No	x (x)	x (x)	x (x)
Headache			
None	x (x)	x (x)	x (x)
Mild	x (x)	x (x)	x (x)
Moderate	x (x)	x (x)	x (x)
Severe	x (x)	x (x)	x (x)
Vitamin A Palmitate Consumption Outside of Study			
Yes	x (x)	x (x)	x (x)
No	x (x)	x (x)	x (x)
Month 2			
Month 3[b]			
Optic Nerve Papilledema			
Study Eye			
Yes	x (x)		
No	x (x)		
Fellow Eye			
Yes	x (x)		
No	x (x)		
Headache			
None	x (x)		
Mild	x (x)		
Moderate	x (x)		
Severe	x (x)		
Vitamin A Palmitate Consumption Outside of Study			
Yes	x (x)		
No	x (x)		

[a] Denominators are the number of participants in the safety population with a non-missing value for the parameter at the specified visit, in the respective cohort or overall. Percentages are rounded to the nearest whole number.
[b] Only participants in Cohort 1 complete Month 3.

Table 21. Summary of Additional Ophthalmic Assessments

Visit / Assessment	Participants with Events N (%)[a]					
	Cohort 1		Cohort 2		Overall	
	Study Eye	Fellow Eye	Study Eye	Fellow Eye	Study Eye	Fellow Eye
Baseline						
Drusen						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes - small	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes - intermediate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes – large	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Hypo/hyper pigmentation						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
RPE detachment						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes - drusenoid	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes – non-drusenoid	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
CNV						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Subretinal/Intraretinal fluid						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Geographic Atrophy						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes - foveal	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes - extra-foveal	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Aphakia						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Pseudophakic lens						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Nuclear Cataract Score						
Not assessed[b]	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Clear	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
< STD2	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
≥ STD2 but < STD3	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
≥ STD3	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Cannot Evaluate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Not Done	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
PSC Cataract Score						
Not assessed[b]	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Clear	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
< STD2	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
≥ STD2 but < STD3	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
≥ STD3	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Cannot Evaluate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Not Done	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

[a] Denominators are the number or participants in the safety population with a non-missing value for the parameter at the specified visit, in the respective cohort or overall. Percentages are rounded to the nearest whole number.
[b] Cataract scores are only assessed in participants without aphakia or pseudophakic lens.
[c] Only participants in Cohort 1 complete Month 3.

Table 21. Summary of Additional Ophthalmic Assessments (continued)

Visit / Assessment	Participants with Events N (%)[a]					
	Cohort 1		Cohort 2		Overall	
	Study Eye	Fellow Eye	Study Eye	Fellow Eye	Study Eye	Fellow Eye
Reticular Pseudodrusen						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Month 1						
Drusen						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes - small	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes - intermediate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes – large	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Hypo/hyper pigmentation						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
RPE detachment						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes - drusenoid	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes – non-drusenoid	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
CNV						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Subretinal/Intraretinal fluid						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Geographic Atrophy						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes - foveal	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes - extra-foveal	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Aphakia						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Pseudophakic lens						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Nuclear Cataract Score						
Not assessed[b]	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Clear	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
< STD2	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
≥ STD2 but < STD3	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
≥ STD3	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Cannot Evaluate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Not Done	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
PSC Cataract Score						
Not assessed[b]	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Clear	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
< STD2	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
≥ STD2 but < STD3	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
≥ STD3	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

[a] Denominators are the number or participants in the safety population with a non-missing value for the parameter at the specified visit, in the respective cohort or overall. Percentages are rounded to the nearest whole number.
[b] Cataract scores are only assessed in participants without aphakia or pseudophakic lens.
[c] Only participants in Cohort 1 complete Month 3.

Table 21. Summary of Additional Ophthalmic Assessments (continued)

Visit / Assessment	Participants with Events N (%)[a]					
	Cohort 1		Cohort 2		Overall	
	Study Eye	Fellow Eye	Study Eye	Fellow Eye	Study Eye	Fellow Eye
Cannot Evaluate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Not Done	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Month 2						
Drusen						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes - small	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes - intermediate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes – large	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Hypo/hyper pigmentation						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
RPE detachment						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes - drusenoid	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes – non-drusenoid	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
CNV						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Subretinal/Intraretinal fluid						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Geographic Atrophy						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes - foveal	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes - extra-foveal	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Aphakia						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Pseudophakic lens						
No	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Yes	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Nuclear Cataract Score						
Not assessed[b]	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Clear	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
< STD2	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
≥ STD2 but < STD3	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
≥ STD3	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Cannot Evaluate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Not Done	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
PSC Cataract Score						
Not assessed[b]	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Clear	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
< STD2	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

[a] Denominators are the number or participants in the safety population with a non-missing value for the parameter at the specified visit, in the respective cohort or overall. Percentages are rounded to the nearest whole number.
[b] Cataract scores are only assessed in participants without aphakia or pseudophakic lens.
[c] Only participants in Cohort 1 complete Month 3.

Table 21. Summary of Additional Ophthalmic Assessments (continued)

Visit / Assessment	Participants with Events N (%)[a]					
	Cohort 1		Cohort 2		Overall	
	Study Eye	Fellow Eye	Study Eye	Fellow Eye	Study Eye	Fellow Eye
≥ STD2 but < STD3	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
≥ STD3	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Cannot Evaluate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Not Done	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Month 3[c]						
Drusen						
No	x (x)	x (x)				
Yes - small	x (x)	x (x)				
Yes - intermediate	x (x)	x (x)				
Yes – large	x (x)	x (x)				
Hypo/hyper pigmentation						
No	x (x)	x (x)				
Yes	x (x)	x (x)				
RPE detachment						
No	x (x)	x (x)				
Yes - drusenoid	x (x)	x (x)				
Yes – non-drusenoid	x (x)	x (x)				
CNV						
No	x (x)	x (x)				
Yes	x (x)	x (x)				
Subretinal/Intraretinal fluid						
No	x (x)	x (x)				
Yes	x (x)	x (x)				
Geographic Atrophy						
No	x (x)	x (x)				
Yes - foveal	x (x)	x (x)				
Yes - extra-foveal	x (x)	x (x)				
Aphakia						
No	x (x)	x (x)				
Yes	x (x)	x (x)				
Pseudophakic lens						
No	x (x)	x (x)				
Yes	x (x)	x (x)				
Nuclear Cataract Score						
Not assessed[b]	x (x)	x (x)				
Clear	x (x)	x (x)				
< STD2	x (x)	x (x)				
≥ STD2 but < STD3	x (x)	x (x)				
≥ STD3	x (x)	x (x)				
Cannot Evaluate	x (x)	x (x)				
Not Done	x (x)	x (x)				

[a] Denominators are the number or participants in the safety population with a non-missing value for the parameter at the specified visit, in the respective cohort or overall. Percentages are rounded to the nearest whole number.
[b] Cataract scores are only assessed in participants without aphakia or pseudophakic lens.
[c] Only participants in Cohort 1 complete Month 3.

Table 21. Summary of Additional Ophthalmic Assessments (continued)

	Participants with Events N (%)[a]					
	Cohort 1		Cohort 2		Overall	
Visit / Assessment	Study Eye	Fellow Eye	Study Eye	Fellow Eye	Study Eye	Fellow Eye
PSC Cataract Score						
Not assessed[b]	x (x)	x (x)				
Clear	x (x)	x (x)				
< STD2	x (x)	x (x)				
≥ STD2 but < STD3	x (x)	x (x)				
≥ STD3	x (x)	x (x)				
Cannot Evaluate	x (x)	x (x)				
Not Done	x (x)	x (x)				

[a] Denominators are the number or participants in the safety population with a non-missing value for the parameter at the specified visit, in the respective cohort or overall. Percentages are rounded to the nearest whole number.
[b] Cataract scores are only assessed in participants without aphakia or pseudophakic lens.
[c] Only participants in Cohort 1 complete Month 3.

LISTINGS

Listing 1. DA Rod Intercept Time in Study Eye from Baseline to Treatment Completion and Post-Treatment Follow-Up

Cohort	Participant ID	Visit[a]	Rod Intercept Time (minutes)	Change from Baseline
1	NEI001	Baseline	x.x	
		Treatment Completion	x.x	x.x
		Post-treatment Follow-up	x.x	x.x
	NEI002	Baseline	x.x	
		Treatment Completion	x.x	x.x
		Post-treatment Follow-up	x.x	x.x
…	…			

[a] Treatment completion visit corresponds to Month 2 in Cohort 1, and Month 1 in Cohort 2. Post-treatment follow-up visit corresponds to Month 3 in Cohort 1, and Month 2 in Cohort 2.

Listing 2. LLVA Total Letters Read in Study Eye from Baseline to Treatment Completion and Post-Treatment Follow-Up

Cohort	Participant ID	Visit[a]	LLVA Total Letters Read	Change from Baseline
1	NEI001	Baseline	x	
		Treatment Completion	x	x
		Post-Treatment Follow-Up	x	x
	NEI002	Baseline	x	
		Treatment Completion	x	x
		Post-Treatment Follow-Up	x	x
…	…			

[a] Treatment completion visit corresponds to Month 2 in Cohort 1, and Month 1 in Cohort 2. Post-treatment follow-up visit corresponds to Month 3 in Cohort 1, and Month 2 in Cohort 2.

Listing 3. LLQ Subscale and Composite Scores from Baseline to Treatment Completion and Post-Treatment Follow-Up

			Driving		Extreme Lighting		Mobility		Emotional Distress		General dim Lighting		Peripheral Vision		Composite Score[a]	
Cohort	Participant ID	Visit[b]	Score	Δ[c]	Score	Δ[c]	Score	Δ[c]	Score	Δ[c]	Score	Δ[c]	Score	Δ[c]	Score	Δ[c]
1	NEI001	Baseline	x.x		x.x		x.x		x.x		x.x		x.x		x.x	
		Treatment Completion	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
		Post-treatment Follow-up	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
	NEI002	Baseline	x.x		x.x		x.x		x.x		x.x		x.x		x.x	
		Treatment Completion	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
		Post-treatment Follow-up	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
…	…															

Score and Δ rounded to the nearest tenth.

[a] Composite score is an average of the six weighted subscale scores.

[b] Treatment completion visit corresponds to Month 2 in Cohort 1, and Month 1 in Cohort 2. Post treatment follow-up visit corresponds to Month 3 in Cohort 1, and Month 2 in Cohort 2.

[c] Δ implies change from baseline.

Figure 1. Study Disposition