NCT01367444

Statistical Analysis Plan

for

The TDU13583 Study Compound:

SAR422459

A Phase I/IIa Dose Escalation Safety Study of Subretinally Injected SAR422459, Administered to Patients with Stargardt's Macular Degeneration

TDU13583

Version 3.0

September 16, 2019

Prepared By:
Coordinating Center
The Emmes Company, LLC
Rockville, Maryland

Reviewer Signature: [redacted]

Reviewer Signature: [redacted]

Reviewer Signature: [redacted]

Coordinating Center Director Signature: [redacted]

TABLE OF CONTENTS

1.0 INTRODUCTION

This statistical analysis plan (SAP) provides details of the proposed statistical analyses for the clinical trial entitled "A Phase I/IIa Dose Escalation Safety Study of Subretinally Injected SAR422459, Administered to Patients with Stargardt's Macular Degeneration." Totally, 12 protocol amendments have been occurred, but Amendment 12 dated November 29, 2018 has not been submitted to study sites for approval. The SAP was updated from Version 2.0 to include updates of baseline definition and cohorts from Amendment 11 and revise some presentations. This document contains a review of the study objectives and design, general statistical considerations, comprehensive statistical analysis methods for safety and biological activity (efficacy) outcomes, and a list of proposed tables and graphs. Any deviation from this SAP will be described and justified in the final study report, as appropriate.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

To assess the safety and tolerability of ascending doses of SAR422459 in patients with Stargardt's Macular Degeneration (SMD).

2.2 Secondary Objective

To evaluate for possible biological activity of SAR422459.

3.0 STUDY DESIGN

This is a phase I/IIa, open-label, dose escalation study to evaluate the safety and tolerability of a single subretinal injection of SAR422459. All patients will be followed for up to 48 weeks. After 48 weeks, patients will enter an open-label, safety study (LTS13588), with follow-up visits, including ophthalmological examinations and recording of adverse events (AEs) for 240 weeks (five years). For a subsequent 10 years, delayed AEs will also be monitored. Details of the assessments and analysis methods for this long-term follow-up study will be discussed in a separate SAP and will be based on the same principles.

A projected total of up to 46 patients will be enrolled in this study, consisting of seven cohorts from five patient groups. The five groups to be used in this study are as follows:

- **Group A:** Patients (18 years or older) with advanced SMD, visual acuity ≤ 20/200 in the worst eye and severe cone-rod dysfunction with no detectable or severely abnormal full-field ERG responses.
- **Group B:** Patients (18 years or older) with SMD, visual acuity ≤ 20/200 in the worst eye

with abnormal full-field ERG responses.

- **Group C:** Patients (18 years or older) with SMD, visual acuity ≤ 20/100 in the worst eye with abnormal full-field ERG responses.
- **Group D:** Patients (from six years to 26 years old) with symptomatic early or childhood-onset SMD (age at disease onset <18 years), and visual acuity ≥ 20/200 in both eyes at the time of the screening visit anticipated to experience rapid deterioration in visual function and/or retinal structure.
- **Group E:** Patients (from six years to 17 years old) with symptomatic SMD and visual acuity ≥ 20/100 in both eyes at the time of the screening visit anticipated to experience rapid deterioration in visual function and/or retinal structure.

The first four cohorts will each consist of four patients and they will be enrolled as part of the initial dose escalation portion of the study. A minimum interval of 21 days between the dosing of the first and subsequent patients in each cohort and a minimum interval of 28 days between cohorts has been selected in order for the Data and Safety Monitoring Board (DSMB) to assess any acute toxicity, post-operative complications and the safety profile of each dose level of SAR422459. The DSMB will be responsible for determining whether to proceed enrolling the next cohort.

Based on data accrual, the DSMB will comprehensively review the safety and tolerability of SAR422459 and make decisions regarding dose escalation, study continuance and recommended amendments to the protocol. If after a minimum interval of 28 days from the dosing of the last patient in a given cohort, the safety and tolerability is considered satisfactory by the DSMB, then the next cohort of patients will be enrolled.

The initial SAR422459 dose to be studied will be 1.8×10^5 transducing units (TU), in 300 µL of vehicle. Dose levels will increase to a maximum of 1.8×10^6 TU.

Four patients from Group A will be initially enrolled into the first cohort and receive the lowest dose of SAR422459 (1.8×10^5 TU). If safety and tolerability are deemed acceptable by the DSMB for this group of patients at the lowest dose (after a minimum of 28 days), then four patients from Group B will be enrolled into the second cohort, also receiving the lowest dose of SAR422459. Cohorts 3 and 4 will also consist of patients belonging to Group B and will receive doses of 6.0×10^5 TU and 1.8×10^6 TU, respectively.

At the end of the dose escalation phase of the study (Cohorts 1-4), if the safety and tolerability of SAR422459 is considered acceptable following DSMB review, six additional patients from Group C (Cohort 5) will be enrolled. For Cohort 5, an interval of 21 days

between dosing the first patient and second patient will be observed; subsequent patients may be enrolled in parallel. If after a minimum interval of 28 days from dosing the last patient of Cohort 5, the safety and tolerability is considered satisfactory by the DSMB then adult patients will be enrolled in Cohort 6 (Group D) and receive SAR422459 at the MTD or the highest dose tested.

Prior to the inclusion of pediatric patients (≥6 and <18 years old), the DSMB will review all safety data including the available data from all cohorts after at least four patients of Cohort 6 have completed 12 weeks of follow-up after having been dosed. An interim report including all available safety data, preliminary efficacy data, analysis of benefit/risk balance of enrolling pediatric patients (with regard to US 21 CFR Part 50 Subpart D 'Additional Safeguards for Children in Clinical Investigations' for FDA specifically) and the recommendations from the DSMB will be submitted for approval to the regulatory authorities and institutional review boards/ethics committees, before enrolling pediatric patients. An interval of 28 days between dosing of the first and second pediatric patients will be observed. Thereafter, subsequent pediatric patients may be enrolled consecutively.

In case patients pass eligibility criteria in both Cohorts 6 and 7, they will be included in Cohort 7.

For Cohorts 6 and 7, to ensure consistency across sites, a centralized review of baseline study assessments will be performed pre-operatively for the purpose of providing a recommendation on the area of the retina to be targeted for the subretinal injection to optimize the treatment benefit.

The SAR422459 doses to be studied are:

Cohort	Group	No. of Patients	Dose Level	Subretinal Injection Vector Total Dose per Eye	Volume
1	A	4	1:10	1.8×10^5 TU	300µL
2	B	4	1:10	1.8×10^5 TU	300µL
3	B	4	1:3	6.0×10^5 TU	300µL
4	B	4	undiluted	1.8×10^6 TU	300µL
5	C	6	undiluted	1.8×10^6 TU (highest dose tested)	300µL
6	D	Up to 12	undiluted	1.8×10^6 TU (highest dose tested)	300µL
7	E	Up to 12	undiluted	1.8×10^6 TU (highest dose tested)	300µL

3.1 Study Stopping Criteria

The following is to be considered stopping enrollment:

- Prolonged anterior chamber inflammation and/or prolonged posterior chamber inflammation continuing without signs of resolution 28 days after SAR422459 administration.

Criteria for suspending enrollment or further study conduct are defined in the DSMB Charter and all events will be reviewed by the DSMB.

In the event that enrollment is terminated, all patients who have been dosed with SAR422459 will continue to be followed up as per protocol until the Week 48 visit has been completed. Thereafter, patients will be encouraged to enroll in a long-term follow-up study.

3.2 Dose Limiting Toxicities

Dosing will stop if a dose-limiting toxicity is encountered in a dosing cohort. Events that constitute a dose-limiting toxicity will be defined by the DSMB Charter. Dose-limiting toxicities include:

- Severe or persistent ocular inflammation;
- Other significant ocular toxicity (e.g., large retinal detachment, evidence of direct toxicity);
- Other systemic toxicities (e.g., acute allergic reaction); and
- Any safety issue that has been identified that adversely changes the benefit/risk balance to study patients.

4.0 TARGETED STUDY POPULATION

The study is multicenter with sites in EU and the USA. Patients with SMD meeting all of the study inclusion criteria and none of the exclusion criteria will be recruited following EC/IRB and regulatory approval. Patients will be classified into groups (A, B, C, D, or E) according to their disease severities at Screening (Day -28). Details regarding the inclusion and exclusion criteria for all patients and by cohort may be found in Section 8.1 of Amendment 11 of the protocol.

5.0 ENDPOINTS

5.1 Primary Endpoints

The primary objective of this study is to evaluate the safety and tolerability of ascending doses of SAR422459 in patients with SMD. Safety and tolerability of the investigational medicinal product (IMP) will be evaluated by the following endpoints:

- The incidence and severity of treatment emergent adverse events (AEs).
- Clinically important changes from baseline in the following safety assessments:
  - Best-corrected visual acuity (BCVA)
  - Slit-lamp examination
  - Fundoscopy/Indirect ophthalmoscopy
  - Fundus photography (color and infrared)
  - Intraocular pressure (IOP)
  - Microperimetry
  - Full-field static perimetry
  - Full-field kinetic perimetry
  - Ocular Coherence Tomography (OCT)
  - Electroretinogram (ERG)
  - Laboratory parameters
  - Vital signs
  - Concomitant medications

For all primary endpoints with repeated measures, the primary time point will be considered the Week 48 visit unless otherwise specified. Last available measures before surgery will be considered as baseline value (e.g., Day -1).

5.2 Secondary Endpoints

The secondary objective is to determine a delay in retinal degeneration following subretinal injection of SAR422459 through changes from baseline in visual function and retinal structure relative to the untreated contralateral eye utilizing the following retinal analytical techniques:

For visual function:

- BCVA
- Microperimetry
- Full-field static perimetry
- Full-field kinetic perimetry

For retinal structure:

- Fundus autofluorescence (FAF)
- OCT

For all secondary endpoints with repeated measures, the primary time point will be considered the Week 48 visit. Last available measures before surgery will be considered as baseline value (e.g., Day -1).

5.3 Other Endpoints

5.3.1 Immunology

Humoral response to SAR422459 vector components.

5.3.2 Biodistribution

SAR422459 distribution in the blood and urine assessed by polymerase chain reaction (PCR). For Cohorts 1-5, blood samples will be taken at Day -28 (Screening), Day 0 (60 minutes post-surgery), Day 1, Weeks 1, 2, 4, 12, 24, 36 and 48 and urine samples will be taken at Day -28 (Screening), Day 0 (60 minutes post-surgery), Day 1, and Weeks 1 and 2. For Cohorts 6-7, blood samples will be taken at Day -28 (Screening), Day 0 (60 minutes post-surgery), Day 1, Weeks 1, 4, 12, 24, and 48 and urine samples will be taken at Day -28 (Screening), Day 0 (60 minutes post-surgery), Day 1, and Week 1 only.

5.3.3 Laboratory Parameters

Hematology, biochemistry, urinalysis and other laboratory data will be measured at various time points throughout the study (refer to Section 2 of the protocol). Values will be flagged as High or Low if outside the laboratory normal range. Out-of-range values will be assessed as clinically significant (CS) or not clinically significant (NCS) by the investigator. CS out-of-range values will be recorded as AEs. Blood for immunology and blood for PCR will also be taken at multiple time points throughout the study, as will urine samples for biodistribution assessment. Shift tables for key laboratory parameters out of normal range will be presented for the assessed visits, if applicable.

5.3.4 Other Safety Parameters

Other safety parameters (vital signs, physical examination) will be measured. New abnormalities will be recorded as AEs.

5.3.5 Exploratory Efficacy Parameters

Contrast sensitivity will be performed using the Sloan Low Contrast Acuity Chart. Reading speed and visual function questionnaires (VFQ-25/CVAQC-25) will be recorded in patients

when possible and if the age of the patient allows. Multifocal ERG and adaptive optics are performed only in Cohorts 1-5 and not required for Cohorts 6-7.

5.4 Other Measures

5.4.1 Concomitant Medication

Changes to concomitant medications will be recorded at all visits.

5.4.2 Patient Characteristics

During screening, height, weight, sex, vital signs, inclusion/exclusion criteria, medical history (including reproductive status, clinical symptoms of SMD and treatment history), ECG, chest X-ray and anesthesia assessment will be recorded.

5.4.3 Withdrawals

The number and percentage of patients who withdraw from the study over time, along with the reasons for withdrawal, will be tabulated.

5.4.4 Deaths

All deaths occurring during the study and its follow-up period will be listed and included in the AE summary.

6.0 GENERAL STATISTICAL CONSIDERATIONS

6.1 Sample Size

This is an exploratory study the primary objective of which is to evaluate safety and, as a secondary objective, to estimate the biological activity. No formal sample size calculation has been performed. Up to a total of 46 patients will be enrolled in seven cohorts. The first four cohorts will consist of four patients each, six additional patients will be enrolled in Cohort 5 at the MTD (1.8×10^6 TU), up to 12 patients will be enrolled into Cohort 6 at the MTD (1.8×10^6 TU), and up to 12 patients will be enrolled in Cohort 7 at the MTD (1.8×10^6 TU).

6.2 Primary Data Set

The primary data set to be used to prepare the final analysis and DSMB reports will include data from all eligible patients, regardless of adherence to the protocol. However, since patients receive only a single treatment, adherence to the protocol will only be affected if patients drop out of the study, are lost to follow-up or if patients are seen outside of the visit windows as defined in the protocol. If a patient withdraws from the study, the Week 48 procedures will be completed where possible.

6.3 Handling Data Irregularities

Although the study will make efforts to ensure maximum patient compliance, data irregularities, including protocol violations, non-compliance, withdrawals, missing values and loss to follow-up, may occur and will impact the proposed analyses. However, the analyses will be primarily descriptive and formal hypothesis testing is not planned. Data which are missing could impact conclusions drawn from even a small number of patients and therefore presentations (tabular and graphical) will include an indication of missing values and, where possible, explanations will be provided. All available data will be reported in DSMB reports. There will be no replacement of missing data and no data will be removed. Data from experimental procedures, or procedures in which patients are unable to provide reliable results (e.g., poor fixation in perimetry), may be presented separately, footnoted, or otherwise indicated in the report.

6.4 Interim Analyses

The DSMB will review accumulating data and evaluate safety of the study prior to escalation to the next dose cohort. No formal interim analyses will be performed, but the following section provides analyses that are specific to DSMB reports.

6.5 Analyses Specific to DSMB Reports

At a minimum, the following individual data and mean data will be presented against time following surgery:

- Adverse events
- Concomitant medications (listed in Patient Profiles)
- Laboratory results
- Humoral antibody response and vector distribution data (whenever possible)
- BCVA
- IOP
- Slit lamp examination and fundoscopy data

Note that additional outcome data may be provided in DSMB reports when available or at the request of the DSMB. Thus, Sections 7 and 8 describe analyses and tables/plots (respectively) that will be selected and presented upon final analyses, and, at a minimum, those relevant to the above outcomes will be provided in DSMB reports.

6.6 Software to be used for Analyses

Data analyses will be conducted using SAS version 9.2 or higher. Some graphs may be generated in R version 3.2.1 or higher.

6.7 Modifications to the statistical section of the protocol

The protocol history table below gives the timing, rationale, and key details of major changes to the protocol statistical sections, including the primary and key secondary endpoints/analyses, and the analysis populations associated with these analyses.

Amendment Number	Date Approved	Rationale	Description of statistical changes
1	14DEC2010	Amended in response to review by the DSMB. Updated exclusion criteria and management of ocular inflammation.	None
2	31MAR2011	Amended in response to review by the FDA. Updated study stopping criteria and injection procedure,	Updated immunology and PCR timepoints.
3	16JUN2011	Amended in response to review by the AFSSAPS.	Clarified patient groups and updated screening/baseline procedures for ERG.
4	24JAN2012	Updated to clarify some discrepancies and add an additional cohort.	Updated time points for reading center endpoints,
5	14APR2014	Updated due to a transfer in study sponsorship.	None
6	12NOV2014	Due to disease progression, reduced the size of Cohort 5 and added Cohort 6, a pediatric cohort.	Added an additional cohort and reduced the size of Cohort 5. Modified timepoints for certain assessments.
7	10MAR2015	Updated definition of rapid deterioration.	None
8	16DEC2015	Clarified target population for Cohort 6 and updated endpoints.	Endpoints updated to be consistent throughout.
9	25FEB2016	Amended in response to review by Health Authorities to modify cohort criteria and address inflammation.	None
10	28JUL2016	Updated inclusion criteria and anti-inflammatory regimen.	None
11	26SEP2017	Added Cohort 7, clarified inclusion criteria, and updated definition of baseline.	Updated definition of baseline to last visit before surgery.

Note: Amendment 12 dated 29NOV2018 has not been submitted to study centers for approval.

6.8 Statistical Modifications made in the Statistical Analysis Plan

The statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the statistical analysis features in the statistical analysis plan.

SAP version number	Date approved	Rationale	Description of statistical changes
1	18NOV2011	Developed to define the analyses to be conducted for DSMB meetings and the CSR.	
2	16SEP2016	Updated for Amendment 10 of the protocol and to add outputs that had been requested by the sponsor.	Added outputs for SAEs, AESIs, AEs by inflammation, AEs related to IMP, and AEs related to procedure. Separated ophthalmic presentation by study and fellow eye and added analyses for fellow eye. Updated patient profile presentations.
3	16SEP2019	Updated for Amendment 11 of the protocol and to include the latest DSMB report format for final study report.	Modified presentations of some outputs and removed patient profile presentations. Updated baseline to be the last visit prior to injection.

7.0 STATISTICAL ANALYSES

In this Phase I/IIa study, statistical analyses will be primarily descriptive and include patient-level reports referred to herein as patient profiles. Although SAR422459 is applied to only the study eye, where available, ophthalmic results for both the study and fellow eyes will be reported and clearly identified as "study" or "fellow." Comparisons between the study and fellow eyes could be biased as the two eyes were not randomized to determine which eye received IMP (the worse eye - as per investigator judgment - is selected as study eye). The following sections describe data presentations which will be available for review prior to proceeding to each cohort and at the end of the study. Some variables (primarily ophthalmic variables) may be combined with others in a patient profile. Refer to Sections 8 and 9 for sample reports.

Data will be summarized using graphical, tabular and/or listing presentations. In addition to patient profiles, continuous-scaled variables will be summarized by mean and standard deviation and/or median and range while categorical variables will be summarized in frequency tables. Percentages given in the summary tables will be rounded and therefore may not always add up to exactly 100 percent.

The primary analysis time point will be 48 weeks following administration of SAR422459, but all results contributing to the primary and secondary outcomes and assessments of safety

at all study visits will be presented. For all outcomes, the last available measures before surgery will be considered as baseline value.

Some data of secondary endpoints and exploratory efficacy endpoints have not been analyzed and included in DSMB summary reports; for example, fundus autofluorescence imaging, reading speed data, CVAQC, and VFQ-25. Likewise, these data will not be analyzed for the final analysis since the abbreviated clinical study report will utilize the latest format of DSMB summary report for the patients enrolled under Amendments 1 to 11 with a data cutoff on May 23, 2018.

7.1 Patient Flow and Compliance

The number of patients screened for eligibility will be reported in a figure, along with the number deemed ineligible at the Screening (Day -28) visit. The reasons for ineligibility will be provided in footnotes.

A summary of patients' compliance to the follow-up schedule and study procedures will also be tabulated. The number (%) of patients completing and withdrawing from the study over time along with reasons for withdrawal, including death, by cohort will be presented in tabular format.

7.2 Baseline Characteristics

Baseline demographic and patient characteristics, including age, height, weight, gender, reproductive status, medical history, ocular history, chest X-ray, physical examination findings, ECG, ophthalmic examination findings (including IOP and visual acuity), imaging parameters and laboratory values, obtained from tests given at Screening (Day -28) and Baseline (Day -1) visits will be summarized. Rapid deterioration criteria and the date of assessment will be listed in a separate table for Cohort 6-7 patients.

7.3 Primary Outcome

The primary outcome is composed of several outcomes related to safety, each of which will be presented at the patient and eye level (refer to Sections 8 and 9). Primary analysis for these outcomes, except adverse events, will compare change in parameter values from Baseline to Week 48. Graphical presentation of cohort summaries will also be presented as described, and clinically important changes from Baseline to Week 48 will be indicated and summarized.

7.3.1 Adverse Events

Adverse events (AEs) will be coded using MedDRA® (last version available at time of database lock). All reported events for all patients, with cohort, event description, event date,

resolution date, severity, outcome, relatedness, SAE indication, duration, High Level Term (HLT), High Level Group Term (HLGT), System Organ Class (SOC) and Preferred Term (PT) will be listed. Specifically, AEs prior to treatment, treatment emergent adverse events (TEAEs) (i.e., started or increased in severity after the patient receives IMP, including abnormal lab results, ECG, etc.) and treatment emergent adverse events (TEAEs) of special interest will be listed separately. An overall summary table of TEAEs will also be provided that includes the number and percentage of TEAEs and patients with at least one TEAE in each dose cohort with:

- A fatal TEAE (death)
- At least one serious TEAE
- At least one severe TEAE
- At least one TEAE related to IMP
- At least one TEAE related to procedure
- Without any TEAEs

In addition, tables will present both the number and percentage of TEAEs and patients with TEAEs by primary SOC, HLGT, HLT, PT, severity and cohort. Treatment emergent adverse events of special interest (TEAESI), detailed in the protocol, will be listed and summarized by primary SOC, HLGT, HLT, PT, severity and cohort. TEAESIs will be indicated where appropriate in the patient profile listing of AEs. AEs related to the IMP and serious adverse events (SAEs) will be indicated in the TEAE listing and described in detail in the body of the report. Specific grouping will be done for events inflammatory in nature in the eye. Summary tables will be presented both with the inflammatory events grouped and without the events grouped. All events with the following preferred terms will be considered inflammatory in nature in the eye:

- Anterior chamber cell
- Anterior chamber inflammation
- Choroidal effusion
- Conjunctivitis
- Eye inflammation
- Eye discharge
- Keratitis
- Macular edema
- Subretinal fluid
- Uveitis
- Vitreous floaters

Patients with at least 1 TEAE will be summarized once by unique MedDRA coded term, where multiple incidences of the same coded term will be counted once only by the most severe event or the event of extreme relationship to the IMP or to study procedure.

7.3.2 Best-Corrected Visual Acuity (BCVA)

BCVA (Early Treatment Diabetic Retinopathy Study [ETDRS] letters read) will be listed by visit and eye. Study and fellow eye mean BCVA will be tabulated by visit and cohort. BCVA for all patients by eye, visit and cohort group will be presented graphically. Mean changes in BCVA by visit and cohort will also be presented graphically. The number of individuals with BCVA gain or loss ≥ 5, ≥ 10 and ≥ 15 letters at any point from baseline to Week 48 will be tabulated by cohort and visit.

7.3.3 Ocular Inflammation

The grading system of ocular inflammation can be found in Appendix A of the study protocol. The inflammatory grades will be treated as ordinal variables and plotted by patient over time. Scores for ocular inflammation, including anterior chamber cells, flare (slit lamp examination) and vitreous cells, haze (indirect ophthalmoscopy) and macular edema, will be listed by eye and shown graphically with other ophthalmic outcomes. Summary counts for the number of 'step-up' and 'step-down' changes in the inflammation scale in the study eye and fellow eye may be tabulated by cohort and visit. Clinically important changes (i.e., ≥ 2 step change) as observed in slit lamp examination and/or indirect ophthalmoscopy from baseline to Week 48 will be indicated and listed where appropriate.

7.3.4 Intraocular Pressure (IOP)

The IOP for each visit will be measured using applanation tonometry. Individual IOP will be listed by eye and shown graphically with other ophthalmic outcomes. IOP will be listed, tabulated and shown graphically similar to BCVA outcomes. Clinically important changes, defined as increases or decreases of ≥ 10 mmHg, and the number of individuals with IOP ≥ 25, ≥ 30 and ≥ 35 mmHg at any point from baseline to Week 48 will be tabulated by cohort and visit.

7.3.5 Microperimetry

Microperimetry images will be used to perform a quantitative assessment of fixation and document scotoma. These image data will not be summarized for Cohorts 1-5 for DSMB meetings; however, appropriate images and/or data values will be reported upon final analyses. Image data will be presented for Cohorts 6-7 for DSMB meetings and upon final analyses.

7.3.6 Full-field Static and Kinetic Perimetry

Full-field static and kinetic perimetry will be used to document scotoma and the level of retinal function for each patient, and clinically significant changes from baseline will be highlighted. For assessments in which more than one measurement is taken at a single visit (e.g., multiple sessions in GATE), the mean of these measurements will be used in analysis.

Individual and mean total volume loss in visual field as well as total volume of full hill of vision will be plotted (dB steradians) over time. Values in each eye will be listed in tabular format by patient and visit. For Cohort 6-7 patients, reliability factor in each eye will be listed in tabular format by patient and visit.

Semi-automated kinetic perimetry (SKP) will be used to estimate total area (degrees^2) of visual field sensitivity and total scotoma area (degrees^2) (for Cohorts 6-7 only) for different stimulus intensity levels (I4e, III4e and V4e isopters). Individual and mean total areas will be plotted against time. Values in each eye will be listed in tabular format by patient and visit. Mean change from Baseline to Weeks 24 and 48 in static and SKP outcomes will be plotted against dose received for each eye (study and fellow).

7.3.7 Optical Coherence Tomography (OCT)

Central macular thickness, subretinal fluid, macular volume and other architectural features will be measured by OCT. Individual values of macular thickness (in the central sub-field) and macular volume will be listed and illustrated graphically similar to other ophthalmic outcomes. Macular thickness and volume will be listed by visit and eye. Macular thickness and volume for all patients' study eye and fellow eye will be presented graphically by visit and cohort. Mean changes in macular thickness and volume by visit and cohort will be summarized in a table and graph by cohort and visit.

Extra parameters will be listed in the patient profiles by patient and visit for Cohort 6-7 patients. These extra parameters include evidence of treatment efficacy, increases in cystoid macular edema from baseline, unfavorable changes in subretinal fluid from baseline, AEs related to the visit and modality, presence of an E-Z Band, and description of E-Z band changes from baseline.

7.3.8 Electroretinogram (ERG)

Full field ERG responses include 30 Hz flicker; photopic single flash a- and b-waves; scotopic cone-rod flash a- and b-waves; and scotopic rod, dim white light b-wave. Amplitudes and implicit times will be presented in tabular format and graphically by patient and cohort as appropriate. Clinically significant changes from baseline in ERG data will be indicated and listed where appropriate.

Maximum peak amplitudes (nV/deg^2) and latency (ms) values for multifocal ERG (mfERG) responses at baseline will be tabulated for each of six concentric rings in the visual field by patient. To examine change in mfERG responses in the central visual field across visits, the mean changes from Baseline across the inner rings (Rings 1-3) will be tabulated and plotted against time by patient. In addition, mean changes across the outer rings (Rings 4-6) will also be tabulated and plotted by patient against time. Multifocal ERG data will be reported only for Cohorts 1-5 and will not be collected for Cohorts 6-7.

7.3.9 Laboratory Parameters

Clinical laboratory results, including hematology (WBC, RBC, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, red cell distribution width, platelets, neutrophils, lymphocytes, monocytes, eosinophils and basophils), blood chemistry (phosphorus, calcium, sodium, chloride, bicarbonate, potassium, fasting blood glucose, creatine phosphokinase and lactate dehydrogenase), kidney and liver function tests (creatinine, blood urea nitrogen, uric acid, ALT, AST, total bilirubin, alkaline phosphatase, total protein, albumin and gamma glutamic transpeptidase and cholesterol), coagulation (prothrombin time and partial thromboplastin time) and urinalysis (protein, blood and ketones) will be listed for each patient and visit in the patient profiles. Individual lab values will be flagged as 'High' or 'Low' if outside the clinical site's normal ranges.

A summary of the number of patients with abnormal and/or clinically significant laboratory values will be provided. The following laboratory values and thresholds will be highlighted to indicate their clinical significance for major functions:

- WBC above 2ULN (upper limit of normal)
- Neutropenia < 1500
- Platelets < 100,000
- Creatinine > 1.5ULN
- ALT ≥ 3ULN
- AST ≥ 3ULN
- Total bilirubin ≥ 2 ULN

The lab values will be assessed by site physicians, and clinically significant abnormal lab values will also be recorded as AEs.

7.3.10 Vital Signs

Vital signs will be summarized and listed by cohort and visit. In addition, patients' vital signs at each study visit will be listed with other examination results in a patient profile. Any

abnormalities that are also clinically significant changes in patients' vital signs will be indicated.

7.3.11 Concomitant Medications

Concomitant medications including the WHO drug coding will be listed by patient, cohort and study visit. Medications will be coded using the last WHO drug coding version available at time of database lock.

7.3.12 Physical Examinations

Physical Examinations will be conducted at Day -28 and Week 48 visits. System abnormality frequencies and percentages (including head/ear-nose-throat, respiratory, gastrointestinal, cardiovascular, musculoskeletal, neurologic, endocrine/metabolic, lymphatic/hematologic, dermatologic, psychological and genitourinary) will be tabulated by cohort at each time point.

7.4 Secondary Outcomes

The secondary outcomes include changes in the study eye from Baseline to Weeks 24 and 48 relative to the untreated, contralateral eye in measures of visual function and retinal structure. The primary outcomes of BCVA, microperimetry, full field static and kinetic perimetry will also serve as secondary outcome measures for visual function. Analysis of these parameters will be conducted as outlined in previous Sections 7.3.2, 7.3.3 and 7.3.6, respectively. Additionally, OCT, a primary outcome measure, and FAF will serve as secondary outcomes measures for retinal structure.

7.4.1 Fundus Autofluorescence (FAF) and Supplementary Reading Center Data

Fundus photography photomontage, fundus autofluorescence (FAF), OCT image data, adaptive optics and microperimetry data will all be analyzed separately by TCTC, the Central Reading Center. These exploratory measures will not be summarized for Cohorts 1-5 for DSMB meetings; however, appropriate images and/or data values will be provided by the Reading Center upon final analyses. FAF and microperimetry data will be presented for Cohorts 6-7 for DSMB meetings and upon final analyses.

7.5 Exploratory Efficacy Outcomes

7.5.1 VFQ-25

All VFQ-25 responses will be re-coded to a scale of 0 to 100 following the scoring rules provided by the questionnaire. The mean of all re-coded scores will determine the score for each patient, which will range from 0 to 100. The scores for the 12 VFQ-25 sub-scales will also be provided, if appropriate. Change in the VFQ-25 responses from baseline to Week 48

will be tabulated by patient and cohort and 95% confidence limits and/or ranges will be provided. Meaningful changes from baseline will be highlighted where appropriate.

The CVAQC-25 will be used for patients under the age of 18. The mean of CVAQC-25 responses will determine the score for each patient. The scores for the seven CVAQC-25 subscales will also be provided, if appropriate. Change in the CVAQC-25 responses from baseline to Week 48 will be tabulated by patient and cohort and 95% confidence intervals and/or ranges will be provided. Meaningful changes from baseline will be highlighted where appropriate.

7.5.2 Reading Speed

Change in reading speed scores (words per minute) as well as changes in log reading acuity determination (logRAD) from baseline to Week 48 will be tabulated by study eye and fellow eye and cohort and 95% confidents limits will be provided as appropriate. Significant changes from baseline to Week 48 will be highlighted where appropriate.

7.5.3 Low-Contrast Sloan Letter Chart Testing

Low-contrast total letters read using the Sloan letter chart will be listed by visit and eye. Study eye and fellow eye mean low-contrast total letters read will be tabulated by visit and cohort. Low-contrast total letters read for all patients by eye, visit and cohort group will be presented graphically. Mean changes in low-contrast letters read by visit and cohort will also be presented graphically. All low-contrast results will be presented at 100% contrast, 2.5% contrast and 1.25% contrast. Low-contrast Sloan letter chart testing will only be performed for Cohort 6-7 patients.

7.6 Other Safety Measures

7.6.1 Immunology

The number and percentage of patients with antibody responses to any SAR422459 component at all time points will be tabulated by dose cohort.

7.6.2 Biodistribution

The number and percentage of patients with SAR422459 detected in the blood and urine by PCR at all relevant time points will be listed (See Section 2 of protocol for specific visits). These data may not be available for review between cohorts but will be reported when available.

7.7 Safety Analysis

The primary, secondary and additional safety measures described in the preceding sections pertain mostly to assessing patient safety. The only additional safety assessment will be the determination of the MTD.

7.7.1 Determination of Maximum Tolerated Dose (MTD)

The MTD will be defined as the highest dose level that has an acceptable safety and tolerability and positive benefit/risk profile in the opinion of the DSMB.

8.0 A LIST OF PROPOSED TABLES/LISTINGS/FIGURES

This section contains a list of proposed tables, listings, and figures that will be presented in analysis of study data, but not all tables, listings, and figures will be included in DSMB reports. At a minimum, tables, listings, and figures from Sections 8.1 through 8.3.4 will be included in DSMB reports, but additional tables, listings, and figures from remaining sections will be included when possible.

8.1 TOC for all TLFs of the latest DSMB report format proposed for TDU13583 CSR

- Table 1A: Screening and Surgery Dates and Visit Completion by Cohort
- Figure 1B: Patient Flow Diagram
- Table 1C: Study Follow-up Completion and Withdrawal (including deaths)
- Table 2A: Demographics Summary by Cohort
- Listing 2B: Detailed Demographic Listing by Cohort
- Listing 2C: Rapid Deterioration Assessment for Cohort 6-7
- Listing 2D: General Medical History by Patient
- Listing 2E: Study Eye Ocular History by Patient
- Listing 2F: Fellow Eye Ocular History by Patient
- Table 2G: Baseline Physical Examination Parameters by Cohort
- Table 2H: Reproductive Status by Patient
- Listing 2I: Detailed Surgery Listing by Patient for All Cohorts
- Listing 2J: Detailed Surgery Listing by Patient for Cohort 6-7 Specific Parameters
- Table 3A: Number and Percentage of Patients Experiencing TEAEs or No Events by Type of Event and Cohort

- Table 3B: Number of Patients Experiencing TEAEs by MedDRA SOC, HLGT, HLT, PT, and Cohort
- Table 3C: Number of Patients with TEAEs of Special Interest by MedDRA SOC, HLGT, HLT, PT, and Cohort
- Table 3D: Number of Patients with SAEs by MedDRA SOC, HLGT, HLT, PT, and Cohort
- Table 3E: Number of Patients Experiencing Inflammatory TEAEs by MedDRA SOC, HLGT, HLT, PT, and Cohort
- Table 3F: Number of Patients with TEAEs Related to IMP by MedDRA SOC, HLGT, HLT, PT, and Cohort
- Table 3G: Number of Patients with TEAEs Related to Procedure by MedDRA SOC, HLGT, HLT, PT, and Cohort
- Table 3H: Listing of Adverse Events Prior to Treatment by Patient and Cohort
- Table 3I: Listing of TEAEs by Patient and Cohort
- Table 3J: Listing of Treatment Emergent Adverse Events of Special Interest by Patient and Cohort
- Table 3K: Listing of Treatment Emergent Serious Adverse Events by Patient and Cohort
- Table 3L: Number of Patients Receiving Concomitant Medications by ATC1, ATC2, ATC3, ATC4, and Cohort
- Listing 3M: Ophthalmic Outcome Listing for Study Eye and Fellow Eye by Patient and Visit
- Table 3N: Mean Changes from Pre-surgical BCVA by Cohort and Visit
- Table 3O: Patients Experiencing a Change in BCVA in the Study Eye at Week 48 Following Treatment by Cohort
- Table 3P: Mean Changes from Pre-surgical IOP by Cohort and Visit
- Table 3Q: Patients Experiencing Elevated IOP in the Study Eye at Week 48 Following Treatment by Cohort
- Table 3R: Patients Experiencing Elevated IOP in the Fellow Eye at Week 48 Following Treatment by Cohort
- Table 3S: Patients Experiencing a Clinically Significant Change in IOP in the Study Eye Following Treatment by Cohort
- Tables 3T-3W: Changes in Ophthalmic Inflammation in the Study Eye by Cohort and Visit
- Figure 3X: BCVA in Study and Fellow Eyes by Patient
- Figure 3Y: IOP in Study and Fellow Eyes by Patient

- Figure 3Z: Mean Changes in BCVA over Time by Cohort
- Figure 3AA: Mean Changes in IOP over Time by Cohort
- Listing 3AB: Listing of Patients with Abnormal and/or Clinically Significant Labs
- Listing 3AC: Abnormal Physical Examination Listing by Patient
- Table 3AD: Mean Change in Continuous Laboratory Parameters by Cohort and Visit
- Figures 3AE-3AZ: Change in Laboratory Parameters by Patient
- Table 3BA: Patients Experiencing Edema or Subretinal Fluid in the study eye by Cohort
- Listing 3BB: OCT Listing by Patient and Visit
- Table 3BC: OCT Central Retinal Thickness (μm) by Cohort and Visit
- Table 3BD: OCT Macular Volume (mm^3) by Cohort and Visit
- Figures 3BE: Central Retinal Thickness (OCT) for Study and Fellow Eyes
- Figures 3BF: Macular Volume (OCT) for Study and Fellow Eyes
- Table 3BG: Change from Baseline in Vital Signs by Cohort and Visit
- Figure 4A: Total Volume Loss Measured by Static (GATE) Perimetry by Patient
- Figure 4B: Volume of Full Field Hill of Vision Measured by Static (GATE) Perimetry by Patient
- Listing 4C: Static (GATE) Perimetry Data by Cohort, Patient, and Visit
- Figures 4D: Semi-Automated Kinetic Perimetry Data in Study Eyes by Patient
- Listing 4E: Kinetic (SKP) Perimetry Data by Cohort, Patient, and Visit
- Figure 4F: Microperimetry Radius of Fixation Data by Patient
- Figure 4G: Microperimetry Mean Sensitivity Data by Patient
- Figure 4H: Microperimetry Eccentricity Data by Patient
- Listing 4I: Microperimetry Data by Cohort, Patient, and Visit
- Listing 4J: Full Field ERG Response (Study Eye) Amplitude and Implicit Time Data by Cohort, Patient and Visit
- Listing 4K: Full Field ERG Response (Fellow Eye) Amplitude and Implicit Time Data by Cohort, Patient and Visit
- Figures 4L-4AL: Full-field ERG Response in Patient X
- Table 4AM: Mean Peak Amplitudes and Latencies at Baseline (mfERG) by Cohort and Patient
- Table 4AN: Central Field (Rings 1-3) Summary mfERG Data by Cohort and Patient
- Table 4AO: Peripheral Field (Rings 4-6) Summary mfERG Data by Cohort and Patient

- Figures 4AP-4AT: Change in Central Field (Rings 1-3) mfERG Response Over Time for Cohort X
- Figures 4AU-4AY: Change in Peripheral Field (Rings 4-6) mfERG Response Over Time for Cohort X
- Table 5A: SAR422459 Positive Immunological Data
- Listing 5B: Detailed Listing of Immunologic Results from Blood Samples by Cohort and Patient
- Listing 5C: Detailed Listing of PCR by Cohort, Patient, and Specimen

8.2 Patient Flow and Compliance

Table 1A will summarize patient compliance with the follow-up schedule. Visits occurring past the protocol required date will be indicated where appropriate. Those that have not yet been completed but remain within the allowed window (See Section 2 of the study protocol) will be highlighted in green.

Table 1A: Screening and Surgery Dates and Visit Completion by Cohort

Patient ID	Cohort	Study Eye	Screen1 Date	Screen2 Date	Surgery Date	Day1 Date	Week1 Date	Week2 Date	Week4 Date	Week12 Date	Week24 Date	Week36 Date	Week48 Date

Figure 1B graphically displays screened patients, patients deemed ineligible at Pre-dose Visit 1 and Pre-dose Visit 2, as well as the reasons for ineligibility. It also reflects eligible patients and those being treated at Day 0.

Figure 1B: Patient Flow Diagram

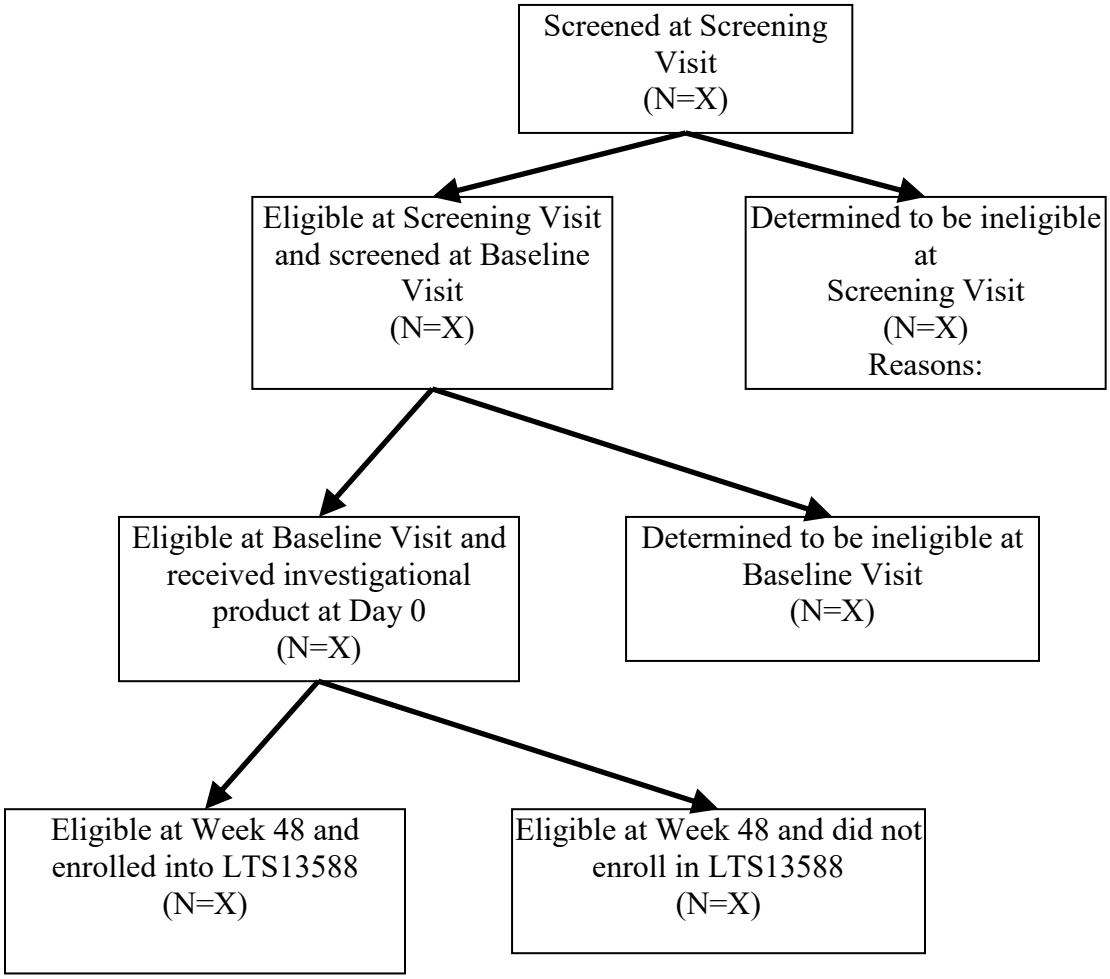


Table 1C will list the overall numbers and percentages of patients completing and withdrawing from the study, and these values will also be stratified by cohort. Reasons for withdrawal, including death, will be provided where applicable.

Table 1C: Study Follow-up Completion and Withdrawal (Including Deaths)

Cohort	Completed TDU13583 (N=X)	Deaths TDU13583 (N=X)	Withdrawals TDU13583 (N=X)
1 (1.8×10^5 TU)			
2 (1.8×10^5 TU)			
3 (6.0×10^5 TU)			
4 (1.8×10^6 TU)			
5 (1.8×10^6 TU)			
6 (1.8×10^6 TU)			
7 (1.8×10^6 TU)			
Total			

8.3 Baseline Characteristics

Table 2A will summarize Baseline demographic information for all patients and stratify the information by cohort.

Table 2A: Demographics Summary by Cohort

		Enrolled Patients (N=X)	Cohort 1 (1.8×10^5 TU) (N=X)	Cohort 2 (1.8×10^5 TU) (N=X)	Cohort 3 (6.0×10^5 TU) (N=X)	Cohort 4 (1.8×10^6 TU) (N=X)	Cohort 5 (1.8×10^6 TU) (N=X)	Cohort 6 (1.8×10^6 TU) (N=X)	Cohort 7 (1.8×10^6 TU) (N=X)
AGE (years)	Median (Range)	X (X-X)	X (X-X)	X (X-X)	X (X-X)	X (X-X)	X (X-X)	X (X-X)	X (X-X)
GENDER	Female	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Male	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
RACE	American Indian or Alaskan Native	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Asian	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Black or African American	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Native Hawaiian or other Pacific Islander	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Other	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	White	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
ETHNICITY	Hispanic or Latino	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Not Hispanic or Latino	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
HEIGHT (cm)	Median (Range)	X (X-X)	X (X-X)	X (X-X)	X (X-X)	X (X-X)	X (X-X)	X (X-X)	X (X-X)
WEIGHT (kg)	Median (Range)	X (X-X)	X (X-X)	X (X-X)	X (X-X)	X (X-X)	X (X-X)	X (X-X)	X (X-X)

Listing 2B will list demographic information by patient.

Listing 2B: Detailed Demographic Listing by Cohort

Cohort	Patient ID	Age (years)	Gender	Race	Ethnicity	Height (cm)	Weight (kg)

Listing 2C lists the rapid deterioration assessment criteria for patients in Cohorts 6-7.

Listing 2C: Rapid Deterioration Assessment for Cohorts 6-7

Patient ID	Loss of ≥1 line of Snellen visual acuity (equivalent to 5 ETDRS letters)	Reduction in macular mean sensitivity of ≥1.2 dB as assessed by microperimetry	Reduction in macular mean sensitivity of ≥5 dB or reduction in hill of vision by >14 dB-sr as assessed by static perimetry	Enlargement in the area of macular RPE atrophy by fundus autofluorescence at a rate of ≥0.5 mm^2	Enlargement in the area of central macular retinal thinning/photoreceptor loss by ocular coherence tomography at a rate of ≥0.5 mm^2

Listing 2D will give a summary of individual patient medical history. Further detailed table(s) may be provided where appropriate.

Listing 2D: General Medical History by Patient

Patient ID	Exam Date	Cardio-vascular	Hematology/ Oncology	Psych-iatric	Gastro-intestinal	Neurologic	Endocrine	Nephrologic	Resp-iratory	Autoimmune	Musculo-skeletal	Allergies	Non-Ocular Surgery

Listings 2E and 2F will include ocular history by patient for the study eye and fellow eye, respectively. Listings 2E and 2F will use the same table shell.

Listing 2E: Study Eye Ocular History by Patient

Patient ID	Exam Date	Study Eye	Cataracts	Glaucoma	Eye Injury	Maculopathy	Pseudovitelliform Macular Degeneration	Stargardt's Macular Degeneration	Retinal Detachment	Sjogren's Disease	Uveitis	VHL	Ocular Herpes	Retinopathy	Myopic Degeneration

Table 2G will summarize baseline physical examination parameters for all patients by cohort. Individual patient profiles will also include physical examination information, laboratory values, vital signs, etc. at baseline as well as during follow-up.

Table 2G: Baseline Physical Examination Parameters by Cohort

		All Eligible Patients (N=X)	Cohort 1 (1.8×10^5 TU) (N=X)	Cohort 2 (1.8×10^5 TU) (N=X)	Cohort 3 (6.0×10^5 TU) (N=X)	Cohort 4 (1.8×10^6 TU) (N=X)	Cohort 5 (1.8×10^6 TU) (N=X)	Cohort 6 (1.8×10^6 TU) (N=X)	Cohort 7 (1.8×10^6 TU) (N=X)
Cardiovascular Assessments	Normal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Abnormal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Dermatologic Assessments	Normal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Abnormal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Endocrine/Metabolic Assessments	Normal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Abnormal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
GI Assessments	Normal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Abnormal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Genitourinary Assessments	Normal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Abnormal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Head/ENT Assessments	Normal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Abnormal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Lymphatic/Hematologic Assessments	Normal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Abnormal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Musculoskeletal Assessments	Normal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Abnormal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Neurologic Assessments	Normal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Abnormal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

		All Eligible Patients (N=X)	Cohort 1 (1.8×10^5 TU) (N=X)	Cohort 2 (1.8×10^5 TU) (N=X)	Cohort 3 (6.0×10^5 TU) (N=X)	Cohort 4 (1.8×10^6 TU) (N=X)	Cohort 5 (1.8×10^6 TU) (N=X)	Cohort 6 (1.8×10^6 TU) (N=X)	Cohort 7 (1.8×10^6 TU) (N=X)
Psychologic Assessments	Normal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Abnormal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Respiratory Assessments	Normal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Abnormal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

Table 2H will give a summary of individual patient reproductive status.

Table 2H: Reproductive Status by Patient

Patient ID	Hysterectomy	Vasectomy	Tubal ligation	Postmenopausal	Other

Listings 2I and 2J will present surgery details by patient. Listing 2J includes data that were only captured for Cohorts 6-7 and will only include Cohort 6-7 data.

Listing 2I: Detailed Surgery Listing by Patient for All Cohorts

Patient ID	Surgery Date	Study Eye	Dose Cohort	Full Dose Administered	Full Dose Not Administered, Specify	Fluid-air Exchange Performed	Air Bubble Removed	Procedure Resulted in Retinal Tear	Complication(s) During Surgery

Listing 2J: Detailed Surgery Listing by Patient for Cohort 6-7 Specific Parameters

Patient ID	Surgery Date	Standard of Care for Pre-operative Assessments	Pre-operative Assessments Completed	Video Recording of the Surgery	Intraoperative OCT Performed	Foveal Detachment	Pars Plana Vitrectomy Performed	Pars Plana Vitrectomy Performed	Bleb Placed According to Recommendation of Centralized Review

Patient profiles will provide notable ocular history at Baseline for each patient in tabular format.

8.4 Primary Outcome Analyses

8.4.1 Adverse Events

Table 3A lists the total and percentage of patients (overall and by cohort) experiencing no TEAEs, any serious TEAEs, a TEAE resulting in death, any TEAE related to IMP or the procedure, and TEAEs by severity. Tables 3B to 3K will include the MedDRA version used for grading as a footnote. All of the AEs presented will be graded using the same MedDRA version. Table 3B summarizes patients with at least one TEAE by MedDRA SOC, HLGT, HLT, PT, and cohort, and Table 3C summarizes patients with treatment emergent AESIs by MedDRA SOC, HLGT, HLT, PT, and cohort. Table 3D summarizes patients with treatment emergent SAEs by MedDRA SOC, HLGT, HLT, PT, and cohort.

Table 3A: Number and Percentage of Patients Experiencing TEAEs or No Events by Type of Event and Cohort

	Patients							
	All (N=X)	Cohort 1 (1.8×10^5 TU) (N=X)	Cohort 2 (1.8×10^5 TU) (N=X)	Cohort 3 (6.0×10^5 TU) (N=X)	Cohort 4 (1.8×10^6 TU) (N=X)	Cohort 5 (1.8×10^6 TU) (N=X)	Cohort 6 (1.8×10^6 TU) (N=X)	Cohort 7 (1.8×10^6 TU) (N=X)
Type of Event								
Fatal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
No Events	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Related to IMP	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Related to Procedure	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Serious	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Mild	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Moderate	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Severe	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

Table 3B: Number of Patients Experiencing TEAEs by MedDRA SOC, HLGT, HLT, PT, and Cohort

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	Cohort 1 (1.8×10^5 TU) (N=X)	Cohort 2 (1.8×10^5 TU) (N=X)	Cohort 3 (6.0×10^5 TU) (N=X)	Cohort 4 (1.8×10^6 TU) (N=X)	Cohort 5 (1.8×10^6 TU) (N=X)	Cohort 6 (1.8×10^6 TU) (N=X)	Cohort 7 (1.8×10^6 TU) (N=X)	All Cohorts (N=X)
Any Class	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
SOC1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
HLGT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
HLT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
PT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
HLT2	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
PT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

Table 3C: Number of Patients with TEAEs of Special Interest by MedDRA SOC, HLGT, HLT, PT, and Cohort

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	Cohort 1 (1.8×10^5 TU) (N=X)	Cohort 2 (1.8×10^5 TU) (N=X)	Cohort 3 (6.0×10^5 TU) (N=X)	Cohort 4 (1.8×10^6 TU) (N=X)	Cohort 5 (1.8×10^6 TU) (N=X)	Cohort 6 (1.8×10^6 TU) (N=X)	Cohort 7 (1.8×10^6 TU) (N=X)	All Cohorts (N=X)
Any Class	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
SOC1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
HLGT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
HLT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
PT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
HLT2	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
PT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

Table 3D: Number of Patients with SAEs by MedDRA SOC, HLGT, HLT, PT, and Cohort

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	Cohort 1 (1.8×10^5 TU) (N=X)	Cohort 2 (1.8×10^5 TU) (N=X)	Cohort 3 (6.0×10^5 TU) (N=X)	Cohort 4 (1.8×10^6 TU) (N=X)	Cohort 5 (1.8×10^6 TU) (N=X)	Cohort 6 (1.8×10^6 TU) (N=X)	Cohort 7 (1.8×10^6 TU) (N=X)	All Cohorts (N=X)
Any Class	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
SOC1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
HLGT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
HLT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
PT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
HLT2	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
PT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

Table 3E summarizes patients with at least one inflammatory TEAE by MedDRA SOC, HLGT, HLT, PT, and cohort.

Table 3E: Number of Patients Experiencing Inflammatory TEAEs by MedDRA SOC, HLGT, HLT, PT, and Cohort

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	Cohort 1 (1.8×10^5 TU) (N=X)	Cohort 2 (1.8×10^5 TU) (N=X)	Cohort 3 (6.0×10^5 TU) (N=X)	Cohort 4 (1.8×10^6 TU) (N=X)	Cohort 5 (1.8×10^6 TU) (N=X)	Cohort 6 (1.8×10^6 TU) (N=X)	Cohort 7 (1.8×10^6 TU) (N=X)	All Cohorts (N=X)
Any Class	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
SOC1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
HLGT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
HLT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
PT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	Cohort 1 (1.8×10^5 TU) (N=X)	Cohort 2 (1.8×10^5 TU) (N=X)	Cohort 3 (6.0×10^5 TU) (N=X)	Cohort 4 (1.8×10^6 TU) (N=X)	Cohort 5 (1.8×10^6 TU) (N=X)	Cohort 6 (1.8×10^6 TU) (N=X)	Cohort 7 (1.8×10^6 TU) (N=X)	All Cohorts (N=X)
HLT2	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
PT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

Tables 3F and 3G summarize patients with at least one TEAE related to IMP and procedure, respectively, by MedDRA SOC, HLGT, HLT, PT, and cohort.

Table 3F: Number of Patients with TEAEs Related to IMP by MedDRA SOC, HLGT, HLT, PT, and Cohort

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	Cohort 1 (1.8×10^5 TU) (N=X)	Cohort 2 (1.8×10^5 TU) (N=X)	Cohort 3 (6.0×10^5 TU) (N=X)	Cohort 4 (1.8×10^6 TU) (N=X)	Cohort 5 (1.8×10^6 TU) (N=X)	Cohort 6 (1.8×10^6 TU) (N=X)	Cohort 7 (1.8×10^6 TU) (N=X)	All Cohorts (N=X)
Any Class	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
SOC1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
HLGT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
HLT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
PT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
HLT2	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
PT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

Table 3G: Number of Patients with TEAEs Related to Procedure by MedDRA SOC, HLGT, HLT, PT, and Cohort

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	Cohort 1 (1.8×10^5 TU) (N=X)	Cohort 2 (1.8×10^5 TU) (N=X)	Cohort 3 (6.0×10^5 TU) (N=X)	Cohort 4 (1.8×10^6 TU) (N=X)	Cohort 5 (1.8×10^6 TU) (N=X)	Cohort 6 (1.8×10^6 TU) (N=X)	Cohort 7 (1.8×10^6 TU) (N=X)	All Cohorts (N=X)
Any Class	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
SOC1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
HLGT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
HLT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
PT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
HLT2	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
PT1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

Tables 3H and 3I list AEs prior to treatment and treatment emergent adverse events (TEAEs), respectively, by patient and cohort. Table 3J lists all adverse events of special interest (AESI), and Table 3K lists all serious adverse events (SAEs).

Table 3H: Listing of Adverse Events Prior to Treatment by Patient and Cohort

								MedDRA Classification		
Cohort	Patient ID	Enroll Date	AE Description	Event Date	Severity of Event	Outcome	Duration (Days)	System Organ Class	High Level Term	Preferred Term

Table 3I: Listing of Treatment Emergent Adverse Events by Patient and Cohort

									Relatedness		MedDRA Classification		
Cohort	Patient ID	Surgery Date	AE Description	Event Date	Outcome	Resolution Date	Duration (Days)	Severity of Event	Relation to Investigational Medicinal Product	Relation to Surgery	System Organ Class	High Level Term	Preferred Term

Table 3J: Listing of Treatment Emergent Adverse Events of Special Interest by Patient and Cohort

									Relatedness		MedDRA Classification		
Cohort	Patient ID	Surgery Date	AE Description	Event Date	Outcome	Resolution Date	Duration (Days)	Severity of Event	Relation to Investigational Medicinal Product	Relation to Surgery	System Organ Class	High Level Term	Preferred Term

Table 3K: Listing of Treatment Emergent Serious Adverse Events by Patient and Cohort

									Relatedness		MedDRA Classification		
Cohort	Patient ID	Surgery Date	AE Description	Event Date	Outcome	Resolution Date	Duration (Days)	Severity of Event	Relation to Investigational Medicinal Product	Relation to Surgery	System Organ Class	High Level Term	Preferred Term

8.4.2 Concomitant Medications

Table 3L summarizes patients with at least one concomitant medication by ATC codes 1, 2, 3, and 4, and cohort.

Table 3L: Number of Patients Receiving Concomitant Medications by ATC1, ATC2, ATC3, ATC4, and Cohort

Anatomic Therapeutic Chemical Classification Level 1 Anatomic Therapeutic Chemical Classification Level 2 Anatomic Therapeutic Chemical Classification Level 1 Anatomic Therapeutic Chemical Classification Level 4	Cohort 1 (1.8×10^5 TU) (N=X)	Cohort 2 (1.8×10^5 TU) (N=X)	Cohort 3 (6.0×10^5 TU) (N=X)	Cohort 4 (1.8×10^6 TU) (N=X)	Cohort 5 (1.8×10^6 TU) (N=X)	Cohort 6 (1.8×10^6 TU) (N=X)	Cohort 7 (1.8×10^6 TU) (N=X)	All Cohorts (N=X)
Any Class	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
ATC1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
ATC2	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
ATC3	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
ATC4	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
ATC3	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
ATC4	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

8.4.3 BCVA, Ocular Inflammation and IOP

Listing 3L lists the primary outcomes of BCVA, ocular inflammation and IOP for the study and fellow eyes by patient and visit, Tables 3M and 3O summarize mean changes in BCVA and IOP, respectively, by cohort and visit for the study and fellow eyes. Table 3N summarizes the number and percentage of individuals with a change (increase or decrease of ≥ 5, >8, ≥ 10, and ≥ 15 letters read) in BCVA in the study eye at Week 48, Table 3P summarizes the number and percentage of individuals with elevated (≥ 25, ≥ 30 and ≥ 35 mmHg) IOP in the study eye, and Table 3R summarizes the number and percentage of individuals with a change (increase or decrease of ≥ 10 mmHg) in IOP in the study eye. Table 3Q will have the same template as Table 3P but will summarize the number and percentage of individuals with elevated (≥ 25, ≥ 30 and ≥ 35 mmHg) IOP in the fellow eye. Changes in anterior chamber inflammation by dose group and visit will be summarized in Tables 3S and 3T, and changes in vitreous inflammation will be summarized in Tables 3U and 3V. BCVA and IOP in study and fellow eyes by patient will be displayed

graphically in Figures 3W and 3S, respectively, in plots similar to Figure 3.1. Mean changes in BCVA and IOP by cohort will be displayed graphically in Figures 3Y and 3Z, respectively, in plots similar to Figure 3.2. Tables and plots will be given for the study eye as well as for the fellow eye and labeled appropriately.

Listing 3L: Ophthalmic Outcome Listing for Study Eye and Fellow Eye by Patient and Visit

		IOP		BCVA		Anterior Cells		Anterior Flare		Vitreous Cells		Vitreous Haze		Macular Edema	
Patient ID	Visit	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow

Table 3M: Mean Changes from Pre-surgical BCVA by Cohort and Visit

		Study Eye					Fellow Eye				
		N	Mean	Std	Min	Max	N	Mean	Std	Min	Max
Cohort	Visit										

Table 3N: Patients Experiencing a Change in BCVA in the Study Eye Following Treatment by Cohort

	BCVA Change >= 5 Letters Read				BCVA Change >8 Letters Read				BCVA Change >= 10 Letters Read				BCVA Change >= 15 Letters Read			
	Increase		Decrease		Increase		Decrease		Increase		Decrease		Increase		Decrease	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Cohort																
1 (1.8×10^5 TU)																
2 (1.8×10^5 TU)																
3 (6.0×10^5 TU)																
4 (1.8×10^6 TU)																
5 (1.8×10^6 TU)																
6 (1.8×10^6 TU)																
7 (1.8×10^6 TU)																
All																

Table 3O: Mean Changes from Pre-surgical IOP by Cohort and Visit

		Study Eye					Fellow Eye				
		N	Mean	Std	Min	Max	N	Mean	Std	Min	Max
Cohort	**Visit**										

Table 3P: Patients Experiencing Elevated IOP in the Study Eye Following Treatment by Cohort

	IOP >= 25 mmHg				IOP >= 30 mmHg				IOP >= 35 mmHg			
	No		Yes		No		Yes		No		Yes	
	N	%	N	%	N	%	N	%	N	%	N	%
Cohort												
1 (1.8×10^5 TU)												
2 (1.8×10^5 TU)												
3 (6.0×10^5 TU)												
4 (1.8×10^6 TU)												
5 (1.8×10^6 TU)												
6 (1.8×10^6 TU)												
7 (1.8×10^6 TU)												
All												

Table 3R: Patients Experiencing a Clinically Significant Change in IOP in the Study Eye Following Treatment by Cohort

	IOP Change >= 10 mmHg			
	Increase		Decrease	
	N	%	N	%
Cohort				
1 (1.8×10^5 TU)				
2 (1.8×10^5 TU)				
3 (6.0×10^5 TU)				
4 (1.8×10^6 TU)				
5 (1.8×10^6 TU)				
6 (1.8×10^6 TU)				
7 (1.8×10^6 TU)				
All				

Tables 3S and 3T: Changes in Anterior Inflammation by Cohort and Visit

		Anterior Chamber Cells						Anterior Chamber Flare					
		No Change		1-Step Increase		2-Step Increase		No Change		1-Step Increase		2-Step Increase	
		N	%	N	%	N	%	N	%	N	%	N	%
Cohort	**Visit**												

Tables 3U and 3V: Changes in Vitreous Inflammation by Cohort and Visit

		Vitreous Cells								Vitreous Haze					
		Decrease		No Change		1-Step Increase		2-Step Increase		No Change		1-Step Increase		2-Step Increase	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Cohort	**Visit**														

Figure 3.1: Ophthalmic Outcomes in Study and Fellow Eyes by Patient

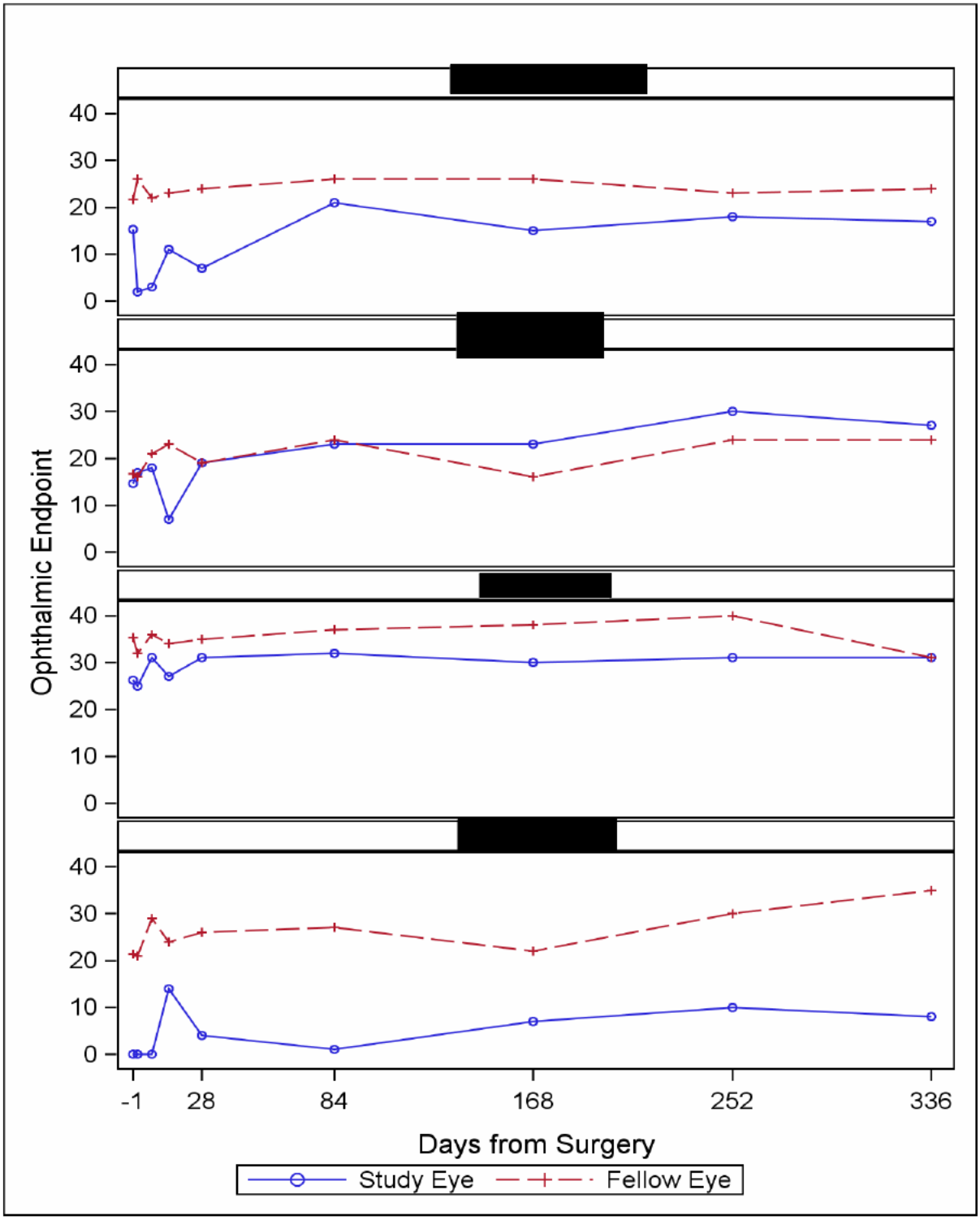
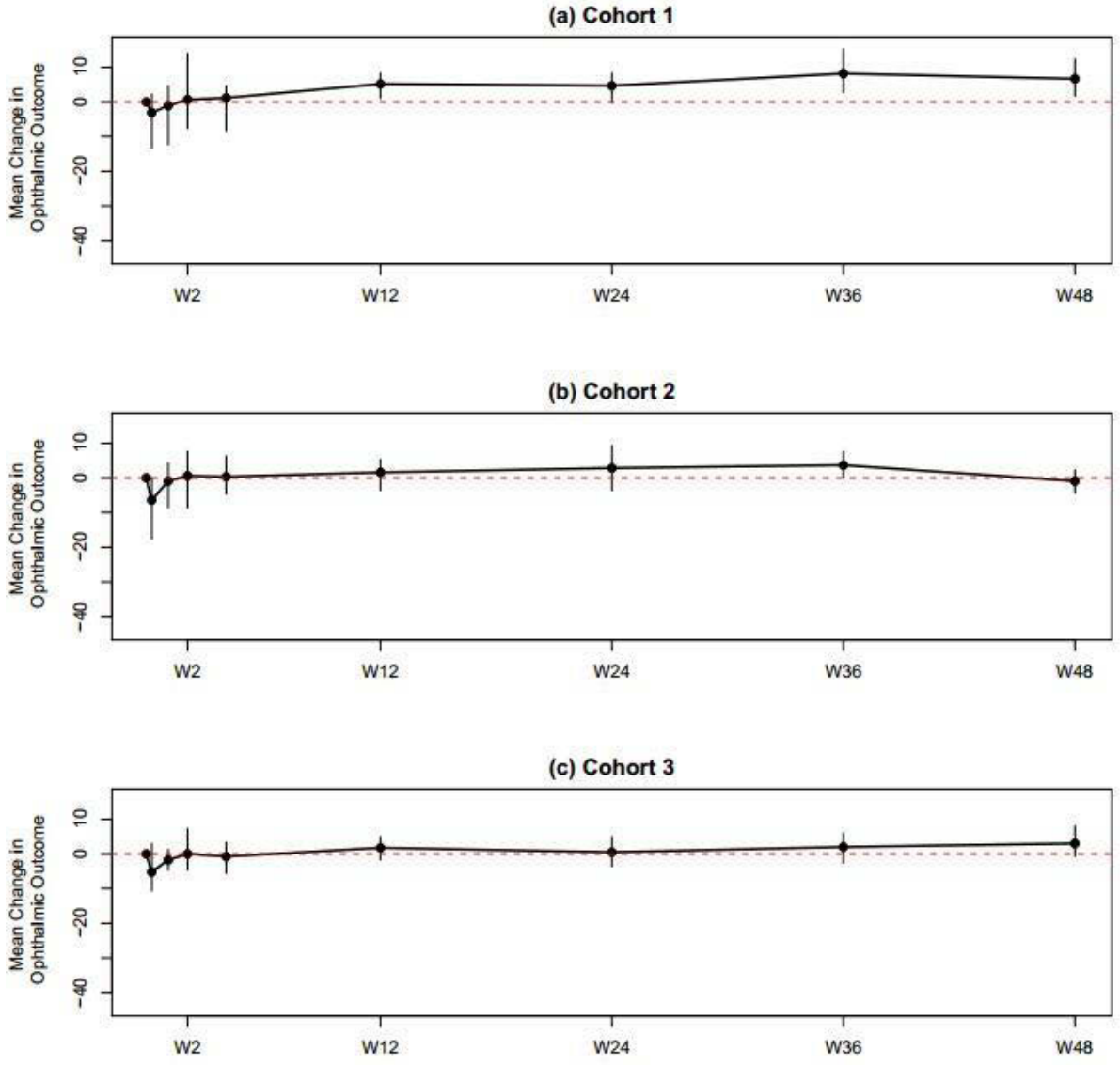


Figure 3.2: Mean Change in Ophthalmic Outcome from Baseline versus Dose Cohort



8.4.4 Laboratory Parameters

Laboratory parameters will be listed for each patient in the patient profiles indicating lab values above or below the clinical site's normal ranges. Listing 3AA lists the patients that had abnormal and/or clinically significant lab values.

Listing 3AA: Listing of Patients with Abnormal and/or Clinically Significant Labs [1]

Site	Patient ID	Age	Gender	Weight (kg)	Visit	Category	Lab	Value	Normal Limits

[1] Lab values that are in bold are clinically significant.

Listing 3AB lists all abnormal physical examination reported by patients during the study.

Listing 3AB: Abnormal Physical Examination Listing by Patient

Cohort	Patient ID	Visit	Head ENT Abnormality	Respiratory Abnormality	Gastrointestinal Abnormality	Cardiovascular Abnormality	Musculoskeletal Abnormality	Neurologic Abnormality

Cohort	Patient ID	Visit	Endocrine/Metabolic Abnormality	Lymphatic/Hematologic Abnormality	Dermatologic Abnormality	Psychologic Abnormality	Genitourinary Abnormality

Table 3AC summarizes mean changes from baseline for each continuous laboratory parameter.

Table 3AC: Mean Change in Continuous Laboratory Parameters by Cohort and Visit

Lab Category	Lab Name (SI Unit)	Cohort	Visit	N	Mean	SD	Quartiles 25%	Quartiles 50%	Quartiles 75%	95% CI Lower	95% CI Upper

Change in continuous laboratory parameters will be presented graphically by patient in Figures 3AD-3AY, in plots similar to Figure 3.1.

8.4.5 OCT

The counts and percentage of patients experiencing edema or subretinal fluid in the study eye at any point in the study will be presented in Table 3AZ.

Table 3AZ: Patients Experiencing Edema or Subretinal Fluid in the Study Eye by Cohort

	Edema				Subretinal Fluid			
	No		Yes		No		Yes	
	N	%	N	%	N	%	N	%
Cohort								
1 (1.8×10^5 TU)								
2 (1.8×10^5 TU)								
3 (6.0×10^5 TU)								
4 (1.8×10^6 TU)								
5 (1.8×10^6 TU)								
6 (1.8×10^6 TU)								
7 (1.8×10^6 TU)								
All								

Listing 3BA lists OCT data by patient. This information will also be included in patient profiles.

Listing 3BA: OCT Listing by Patient and Visit

		Central Macular Thickness		Macular Volume		Edema		Subretinal Fluid		Comments	
Patient ID	Visit	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow

Summary statistics for central retinal thickness and macular volume by cohort and visit for the study and fellow eyes as measured using OCT will be presented in Tables 3BB and 3BC, respectively. Figures 3BD and 3BE, similar to Figure 3.1, will also be used to summarize central retinal thickness and macular volume, respectively, in study and fellow eyes.

Table 3BB: OCT Central Retinal Thickness (µm) by Cohort and Visit

		Study Eye					Fellow Eye				
		N	Mean	Std	Min	Max	N	Mean	Std	Min	Max
Cohort	Visit										
X (Dose TU)	Screening										
	Baseline										
	Day 1										
	Week 1										
	Week 2										
	Week 4										
	Week 12										
	Week 24										
	Week 36										
	Week 48										

Table 3BC: OCT Macular Volume (mm^3) by Cohort and Visit

		Study Eye					Fellow Eye				
		N	Mean	Std	Min	Max	N	Mean	Std	Min	Max
Cohort	Visit										
X (Dose TU)	Screening										
	Baseline										
	Day 1										
	Week 1										
	Week 2										
	Week 4										
	Week 12										
	Week 24										
	Week 36										
	Week 48										

8.4.6 Vital Signs

Table 3BF summarizes median vital signs by cohort and by visit. A listing of vital signs by visit will be provided in each patient's profile report. Clinically significant changes or abnormalities will be noted.

Table 3BF: Change from Baseline in Vital Signs by Cohort and Visit

		Temperature Median (Min, Max)			Blood Pressure Median (Min, Max)		
Cohort	Visit	Degrees Fahrenheit	Degrees Celsius	Respiration Median (Min, Max)	Systolic	Diastolic	Pulse Median (Min, Max)

8.5 Secondary Outcomes

8.5.1 Full-field Kinetic and Static Perimetry

Figures 4A and 4B will present total volume loss and volume of full field hill of vision, respectively, measured by static (GATE) perimetry in the study and fellow eyes of all patients, in plots similar to Figure 3.1. Figure 4D will present semi-automated kinetic perimetry data in the study eye of all patients, in plots similar to Figure 3.1. Listings 4C and 4E display static (GATE) and kinetic (SKP) data, respectively, by cohort, patient and visit for both study and fellow eyes.

Listing 4C: Static (GATE) Perimetry Data by Cohort, Patient and Visit

Cohort	Patient ID	Visit	Total Volume Loss (Decibel Steradians)		Volume of Full Field Hill of Vision (Decibel Steradians)		Reliability Factor (Cohort 6 only)	
			Study	Fellow	Study	Fellow	Study	Fellow

Listing 4E: Kinetic (SKP) Perimetry Data by Cohort, Patient and Visit

Cohort	Patient ID	Visit	I4E Isopter Area (Squared Degrees)		III4E Isopter Area (Squared Degrees)		V4E Isopter Area (Squared Degrees)		I4E Scotoma Area (Squared Degrees) (Cohort 6 only)		III4E Scotoma Area (Squared Degrees) (Cohort 6 only)		V4E Scotoma Area (Squared Degrees) (Cohort 6 only)	
			Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow

8.5.2 Microperimetry

Figures 4F, 4G, and 4H will present radius of fixation, mean sensitivity, and eccentricity, respectively, measured by microperimetry in the study and fellow eyes of all patients, in plots similar to Figure 3.1. Listing 4I displays microperimetry data by cohort, patient and visit for both study and fellow eyes. Microperimetry data were collected only for Cohorts 6-7.

Listing 4I: Microperimetry Data by Cohort, Patient and Visit

			Follow-up Mode Used		Radius of Fixation (degrees)		Mean Sensitivity (dB)		Eccentricity (dB)	
Cohort	Patient ID	Visit	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow

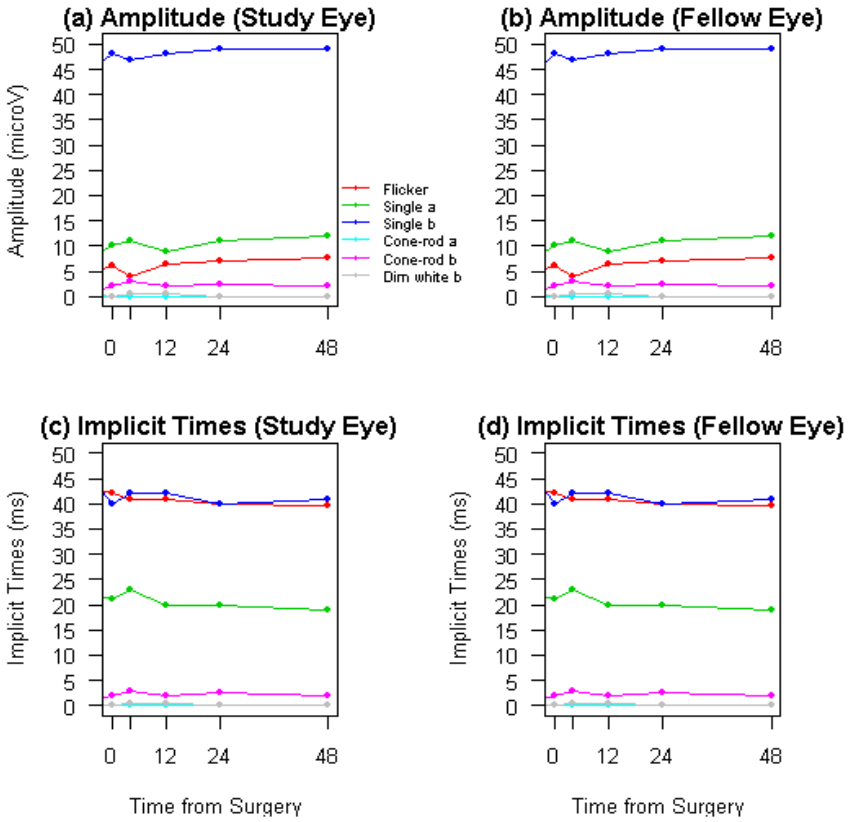
8.5.3 ERG

Listing 4J lists full-field ERG parameters for Cohorts 1-5 by patient. Response amplitudes (microvolts) and implicit times (ms) are listed for the study eye. Response amplitudes (microvolts) and implicit times (ms) for the fellow eye will be listed separately in Listing 4K. The a- and b- wave amplitudes and implicit times will be represented graphically, similarly to Figure 4.1, by patient in Figures 4L-4AL. Clinically significant changes from Day -1 in ERG data will be indicated and listed where appropriate.

Listing 4J: Full Field ERG Response (Study Eye) Amplitude and Implicit Time Data by Cohort, Patient and Visit

			30 Hz Flicker		Photopic Single Flash (a-wave)		Photopic Single Flash (b-wave)		Scotopic Cone-Rod (a-wave)		Scotopic Cone-Rod (b-wave)		Scotopic Rod (dim, b-wave)	
Cohort	Patient ID	Visit	Amp	Imp Time	Amp	Imp Time	Amp	Imp Time	Amp	Imp Time	Amp	Imp Time	Amp	Imp Time

Figure 4.1: Full Field ERG Response



Tables 4AM, 4AN and 4AO list the mean peak amplitude and latencies for each patient at Baseline for each ring, mean changes in these values for the central (Rings 1-3) visual field and mean changes for the peripheral (Rings 4-6) visual field, respectively, for Cohorts 1-5. Figures 4AP-4AT illustrate the change in peak and latency values for the central visual field against time for each patient in Cohorts 1-5, in plots similar to Figure 4.2. Figures 4AU-4AY illustrate the change in peak and latency values for the peripheral visual field against time for each patient in Cohorts 1-5, in plots similar to Figure 4.3.

Table 4AM: Mean Peak Amplitudes and Latencies at Baseline (mfERG) by Cohort and Patient

			Ring 1		Ring 2		Ring 3		Ring 4		Ring 5		Ring 6	
Cohort	Patient ID	Study Eye	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS

Table 4AN: Central Field (Rings 1-3) Summary mfERG Data by Cohort and Patient

			Mean Central Field (Baseline)		Mean Change (Week 4)		Mean Change (Week 12)		Mean Change (Week 24)		Mean Change (Week 48)	
Cohort	Patient ID	Study Eye	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS

Table 4AO: Peripheral Field (Rings 4-6) Summary mfERG Data by Cohort and Patient

			Mean Peripheral Field (Baseline)		Mean Change (Week 4)		Mean Change (Week 12)		Mean Change (Week 24)		Mean Change (Week 48)	
Cohort	Patient ID	Study Eye	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS

Figure 4.2: Change in Central Field (Rings 1-3) mfERG Response Over Time for Cohort X

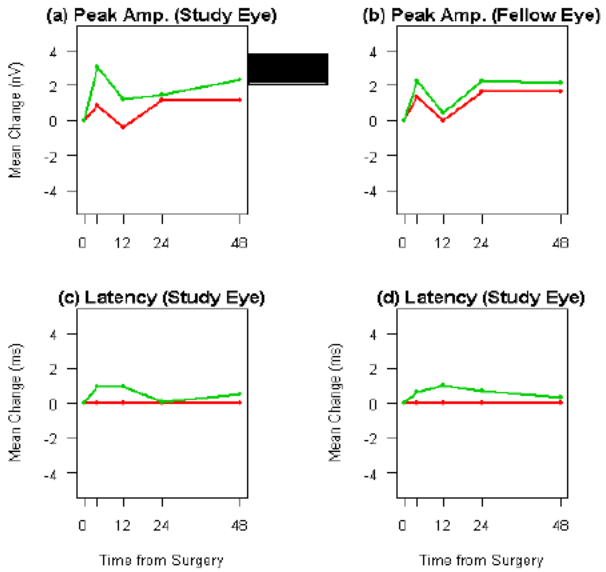
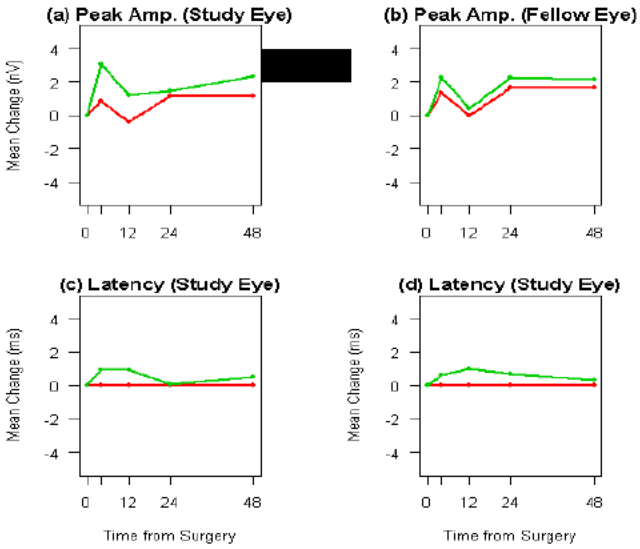


Figure 4.3: Change in Peripheral Field (Rings 4-6) mfERG Response Over Time for Cohort X



8.5.4 Fundus Autofluorescence

Listing 4AZ lists FAF data by patient. This information will also be included in patient profiles. Figures similar to 3.1 and 3.2 may also be used to summarize continuous FAF outcome variables. The data have not been analyzed for DSMB reports.

Listing 4AZ. Fundus Autofluorescence Data by Patient and Visit

		Same Area of the Retina Imaged as Compared to Baseline		Number of Regions		Total Identified Area of Atrophy (mm^2)		Best Exposure		Phenotype		Comments	
Patient ID	Visit	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow

8.5.5 VFQ-25

At the end of the study, change in VFQ-25 scores will be tabulated by cohort (Table 4BA) and by patient (Table 4BB). For Cohorts 6-7, change in CVAQC-25 score will be tabulated (Table 4BC) and listed by patient (Table 4BD). VFQ-25 and CVAQC-25 scores may be summarized using plots similar to those in Figures 3.1 and 3.2. The data have not been analyzed for DSMB reports.

Table 4BA: Change in VFQ-25 by Cohort

Cohort	Mean Change in VFQ-25 Score	95% Confidence Limits

Table 4BB: Change in VFQ-25 by Patient

Cohort	Patient ID	Baseline VFQ-25 Score	Week 48 VFQ-25 Score	Change in VFQ-25 Score

Table 4BC: Change in CVAQC-25 in Cohorts 6-7

Cohort	Mean Change in CVAQC-25 Score	95% Confidence Limits

Table 4BD: Change in CVAQC-25 by Patient

Cohort	Patient ID	Baseline CVAQC-25 Score	Week 48 CVAQC-25 Score	Change in CVAQC-25 Score

8.5.6 Reading Speed

At the end of the study, change in reading speed scores (words per minute) and changes in logRAD will be tabulated by cohort (Table 4BE) and by study eye and fellow eye (Listing 4BF). Reading speed may be summarized using plots similar to those in Figures 3.1 and 3.2. The data have not been analyzed for DSMB reports.

Table 4BE: Change in Reading Speed Outcomes by Cohort

	Mean Change in Reading Speed (words per minute)			95% Confidence Limits for Mean Change in Reading Speed			Mean Change in logRAD		95% Confidence Limits for Mean Change in logRAD	
Cohort	Study	Fellow	OU	Study	Fellow	OU	Study	Fellow	Study	Fellow

Listing 4BF: Change in Reading Speed Score by Patient

		Baseline Reading Speed (words per minute)			Week 48 Reading Speed (words per minute)			Baseline logRAD		Week 48 logRAD	
Cohort	Patient ID	Study	Fellow	OU	Study	Fellow	OU	Study	Fellow	Study	Fellow

8.5.7 Low-Contrast Sloan Letter Chart Testing

Listing 4BG lists the low-contrast total letters read for the study and fellow eyes by patient and visit and Table 4BH summarizes mean changes in low-contrast total letters read by cohort and visit for the study and fellow eyes. Low-contrast Sloan letter chart outcome data may be displayed graphically in plots similar to Figures 3.1 and 3.2. Low-contrast total letters read data will only be collected and presented for Cohort 6-7 patients. The data have not been analyzed for DSMB reports.

Listing 4BG: Low-Contrast Sloan Letter Chart Total Letters Read for Study Eye and Fellow Eye by Patient and Visit

		100% Contrast		2.5% Contrast		1.25% Contrast	
Patient ID	Visit	Study	Fellow	Study	Fellow	Study	Fellow

Table 4BH: Mean Changes from Pre-surgical Low-Contrast Letters Read by Cohort and Visit

		Study Eye					Fellow Eye				
		N	Mean	Std	Min	Max	N	Mean	Std	Min	Max
Cohort	Visit										

8.6 Other Endpoints

Summary reports from the immunological and biodistribution endpoint data will be provided. Tables similar to those seen in the following sections may also be provided to supplement these reports. Table 5A lists all timepoints where patients had a positive ELISA response. Listing 5B lists all immunologic results by cohort and patient. Listing 5C lists all biodistribution data by cohort and patient.

8.6.1 Immunology

Table 5A: SAR422459 Positive Immunological Data

Cohort	Patient ID	Immunological Report Date	Visit	ELISA Assay Result (RU)-Baseline	ELISA Assay Result (RU)-Post Admin	Positive/Negative ELISA Response	Western Blot Required	Positive/Negative Western Blot Result

Listing 5B: Detailed Listing of Immunologic Results from Blood Samples by Cohort and Patient

Cohort	Patient ID	Immunological Report Date	Visit	ELISA Assay Results (RU)		Positive/ Negative ELISA Response	Western Blot Required	Positive/Negative Western Blot Result
				Baseline	Post-Admin			

8.6.2 Biodistribution Endpoint

Listing 5C: Detailed Listing of PCR by Cohort, Patient and Specimen

(result includes the actual quantitative result or one of ND (negative), NQ < LLOQ (not quantifiable, < lower level of quantitation), or a shaded box indicating that the result was not available.)

Cohort	Patient ID	Specimen	Screening	Day 0	Day 1	Week 1	Week 2	Week 4	Week 12	Week 24	Week 36	Week 48
		Plasma										
		Buffy coat										
		Urine										