Statistical Analysis Plan

for

The TDU13600 Study

Compound: SAR421869

A Phase I/IIa Dose Escalation Safety Study of Subretinally Injected UshStat, Administered to Patients with Retinitis Pigmentosa Associated with Usher Syndrome Type 1B

TDU13600

Version 2.0

July 22, 2016

Prepared By:
Coordinating Center
The Emmes Corporation
Rockville, Maryland

Reviewer Signature:	[redacted]	Date: 22/7/16
Reviewer Signature:		Date: 22JUL2016
Reviewer Signature:		Date: 22JUL2016
Coordinating Center Director Signature:		Date: 22JUL2016

TABLE OF CONTENTS

TABLE OF CONTENTS (CONTINUED)

1.0 INTRODUCTION

This statistical analysis plan provides details of the proposed statistical analyses for the clinical trial entitled "A Phase I/IIa Dose Escalation Safety Study of Subretinally Injected UshStat, Administered to Patients with Retinitis Pigmentosa Associated with Usher Syndrome Type 1B." Study number TDU13600. This document contains a review of the study objectives and design, general statistical considerations, comprehensive statistical analysis methods for efficacy and safety endpoints, and a list of proposed tables and graphs. Any deviation from this statistical analysis plan will be described in the final study report, as appropriate.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the safety and tolerability of ascending doses of subretinal injections of UshStat in patients with Usher syndrome type 1B.

2.2 Secondary Objective

To evaluate possible biological activity of UshStat.

3.0 STUDY DESIGN

This is a Phase I/IIa open-label dose escalation study of subretinally injected UshStat in patients with Usher's retinitis pigmentosa (RP). All patients will be followed for 48 weeks. After 48 weeks, patients will enter an open-label safety study, and long-term follow-up visits, including ophthalmological examinations and recording of Adverse Events (AEs), will continue 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.

A projected total of up to 18 patients will be enrolled in this study, consisting of five dose cohorts. The study is separated into a dose escalation phase, Part A (Cohorts 1, 2 and 3), followed by two dose extension phases at the maximum tolerated dose (MTD), Parts B (Cohort 4) and C (Cohort 5). Part A will evaluate three ascending dose levels of UshStat in 300 µL of vehicle. Up to nine patients will be enrolled in Part A, three patients per dose cohort. All patients enrolled in Part A must be at least 18 years of age, have clinical and molecular diagnosis of RP associated with Usher syndrome type 1B caused by *MYO7A* mutation(s), exhibit concentric constriction of kinetic visual field centrally in the worse seeing eye to ≤20 degrees confirmed by visual field measurement by Semi-automated Kinetic Perimety (SKP), and have no detectable rod-derived amplitudes on full-field electroretinogram (ERG).

In Part A 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 DSMB to assess any acute toxicity, post-operative complications and the safety profile at each dose level of UshStat. The DSMB will be responsible for determining whether to proceed enrolling the next cohort of patients. Based on accrual of the data, the DSMB will comprehensively review the safety and tolerability of UshStat and make the 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 third patient in a given cohort, the safety and tolerability is considered satisfactory by the DSMB, then the next cohort of three patients will be enrolled. The maximum tolerated dose (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.

If the safety and tolerability is considered satisfactory by the Data Safety and Monitoring Board (DSMB), regulatory authorities and institutional review boards (IRB) / independent ethics committees (EC) in Part A of the study, then the study will proceed to Part B that may enroll a maximum of three patients in parallel.

Patients enrolled in Part B must be at least 18 years old, have RP associated with Usher syndrome type 1B caused by *MYO7A* mutation(s), exhibit concentric constriction of kinetic visual field centrally in the worse seeing eye equating to a horizontal visual field diameter of >20 degrees confirmed by visual field measurement by Semi-automated Kinetic Perimetry (SKP), exhibit visual field loss in the worse seeing eye that is equivalent to at least 30% reduction from normal sensitivity volume (decibel-steradians) on full-field German Adaptive Thresholding Estimation (GATE) Static Perimetry using the size V test target, and have no detectable rod-derived amplitudes on full field ERG.

Part C provides the opportunity to extend the study to include pediatric patients at least six years of age. Prior to inclusion of pediatric patients, the DSMB will review all safety data three months after all three patients in Cohort 4 have been dosed. An interim report including all available safety data, preliminary efficacy/activity data and the recommendations from the DSMB will be submitted to regulatory agencies and institutional review boards/ethics committee for review before patients of at least six years of age will be included in Part C of the study (Cohort 5).

The UshStat doses to be studied are:

			Subretinal Injection	
Part A				
	Cohort	**Age**	**Number of patients**	**Vector total dose per eye**	**Volume**
	1	≥18	3	1.4 x 10^5 TU	300µL
	2	≥18	3	4.7 x 10^5 TU	300µL
	3	≥18	3	1.4 x 10^6 TU	300µL
Part B					
	4	≥18	3	MTD	300µL
Part C					
	5	≥6	Up to 6	MTD	300µL

The initial UshStat dose to be studied will be 1.4×10^5 transducing units (TU), in 300 µL of vehicle. Dose levels will increase to a maximum of 1.4×10^6 TU. 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.

Patients will be allocated to active treatment (UshStat), in the order in which they are enrolled into the study. A minimum of 21 days must be allowed between dosing of the first and subsequent patients in any cohort, and a minimum of 28 days must be allowed between the final patient of one cohort and the first patient of the subsequent cohort. Three patients (with 21 days of follow-up between the first and subsequent patients) will be initially enrolled into the first cohort and receive the lowest dose of study drug (1.4×10^5 TU). If the DSMB agrees safety and tolerability are acceptable for this group of patients at the lowest dose (after a minimum of 28 days), then three more patients will be enrolled into the second cohort, receiving the next dose of UshStat (4.7×10^5 TU). Patients in Cohort 3 will receive a dose of 1.4×10^6 TU of investigational medicinal product (IMP), in accordance with the procedures outlined in the preceding paragraph.

Following determination of the MTD and review of the Part A study data by the DSMB and the appropriate regulatory authorities (IRB/EC), three patients will be enrolled in parallel at the MTD in Part B (Cohort 4). Finally, the DSMB will review all safety data three months after all three patients in Cohort 4 have been dosed, and regulatory agencies and IRB/EC will review an interim report including all available safety data, preliminary efficacy/activity data and the recommendations from the DSMB. Patients of at least six years of age will be included in Part C of the study (Cohort 5).

3.1 Study Stopping Criteria

The following are considered stopping criteria:

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

Criteria for suspending enrolment or further study conduct are defined in the DSMB Charter and all events will be reviewed by the DSMB. In the event of early study termination, all patients who have been dosed with UshStat will continue to be followed-up as per protocol. In addition, the study enrolment may be terminated at any time at the request of the Food and Drug Administration (FDA), the IRB/EC, the primary investigator (PI), or Sponsor.

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 are 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);
- Any safety issue that has been identified that adversely changes the benefit/risk balance to study participants.

4.0 TARGETED STUDY POPULATION

Patients will be recruited from the hospitals' Usher syndrome type 1B patient population following IEC/IRB and regulatory approval. Up to 18 patients of either sex with Usher syndrome type 1B will be enrolled. This is a multicenter study with sites in the USA and EU. The selected sites have extensive experience in ophthalmic surgery, intraocular injections and handling of gene therapy products.

4.1 Inclusion Criteria

4.1.1 Main Inclusion Criteria

Patients must meet ALL of the following criteria to be considered for enrolment into this study.

1. Signed and dated written informed consent must be obtained from the patient (or assent in the case of minors from their legal guardian/representative), in accordance with the local regulations.
2. Clinical and molecular diagnosis of RP associated with Usher syndrome type 1B, caused by at least one pathogenic *MYO7A* mutation on both alleles, confirmed by direct sequencing and co-segregation analysis within the patient's family.

3. Patients must have suitable verbal/auditory and/or tactile sign language communication (in the opinion of the investigator) as to allow written informed consent to be obtained.
4. Females of childbearing potential must have a negative urine pregnancy test at screening and at baseline, and agree to use an effective form of contraception such as the contraceptive pill or intra uterine device for at least three months following UshStat administration, or be surgically sterile or postmenopausal, with the last menstrual period being over two years prior to enrollment.
5. Males of reproductive potential must agree with their partner to use two forms of contraception, including one barrier method for at least three months following UshStat administration if their partner is of childbearing capacity, or must be surgically sterile.

Partners of study patients should use barrier contraception for at least three months after UshStat administration.

4.1.2 Specific Inclusion Criteria for Cohorts 1, 2 and 3

- ≥18 years of age;
- Concentric constriction of kinetic visual field centrally in the worse seeing eye equating to a horizontal visual field diameter of ≤20 degrees, measured through the center of the visual field grid. The visual field constriction will be measured by Semi-automated Kinetic Perimetry (SKP) and the degrees of constriction will be confirmed by centralized independent assessment of the SKP data;
- No detectable rod-derived amplitudes on the full field electroretinogram performed to ISCEV standards.

4.1.3 Specific Inclusion Criteria for Cohort 4

- ≥18 years of age;
- Concentric constriction of kinetic visual field centrally in the worse seeing eye equating to a horizontal visual field diameter of >20 degrees, measured through the center of the visual field grid. The visual field constriction will be measured by Semi-automated Kinetic Perimetry (SKP) and the degrees of constriction will be confirmed by centralized independent assessment of the SKP data;
- Visual field loss in the worse seeing eye that is equivalent to ≥30% reduction from normal sensitivity volume (decibel-steradian) on full-field GATE Static Perimetry using the size V (1.7°) test target. The percentage reduction in normal sensitivity volume will be confirmed by centralized independent assessment of the data;
- No detectable rod-derived amplitudes on the full field electroretinogram performed to ISCEV standards.

4.1.4 Specific Inclusion Criteria for Cohort 5

- ≥6 years of age;
- Concentric constriction of kinetic visual field centrally in the worse seeing eye equating to a horizontal visual field diameter of >20 degrees, measured through the center of the visual field grid. The visual field constriction will be measured by Semi-automated Kinetic Perimetry (SKP) and the degrees of constriction will be confirmed by centralized independent assessment of the SKP data;
- Visual field loss in the worse seeing eye that is equivalent to ≥30% reduction from normal sensitivity volume (decibel-steradian) on full-field GATE Static Perimetry using the size V (1.7°) test target. The percentage reduction in normal sensitivity volume will be confirmed by centralized independent assessment of the data;
- No detectable rod-derived amplitudes on the full field electroretinogram performed to ISCEV standards.

4.2 Exclusion Criteria

ANY one of the following criteria will exclude patients from being enrolled into the study:

1. Presence of significant ocular abnormalities in the study eye that in the opinion of the investigator would preclude the planned surgery, effective safety follow-up, or interfere with the interpretation of study endpoints (e.g. glaucoma, corneal or significant lens opacities, pre-existing uveitis, intraocular infection, choroidal neovascularization).
2. Any pre-existing factor or past history of eye disease in children that may predispose to an increased risk of surgical complications in the study eye (e.g. trauma, previous surgery, uveitis, congenital, developmental or structural abnormalities).
3. Concomitant systemic diseases including those in which the disease itself, or the treatment for the disease, can alter ocular function (e.g. malignancies, diabetes, juvenile rheumatoid arthritis or sickle-cell disease).
4. Any ocular surgery including laser and cataract surgery with intraocular lens implantation, aphakia or prior vitrectomy, in the study eye within six months of screening.
5. Any contraindication to pupil dilation in either eye.
6. Treatment with intravitreal, subtenon, or periocular steroid within four months of the screening visit.
7. Any known allergy to any component of the delivery vehicle or diagnostic agents used during the study (e.g. fluorescein, dilation drops), or medications planned for use during the peri-operative period, particularly topical, injected or systemic corticosteroids.
8. Life-threatening illness.

9. Alcohol or other substance abuse.
10. Laboratory test abnormalities or abnormalities in electrocardiogram or chest X-ray, that in the opinion of the principal investigator, are clinically significant and would make the patient unsuitable for participation in the study.
11. Intercurrent illness or infection 28 days prior to UshStat administration.
12. Contraindications to use of anesthesia (local or general, as appropriate).
13. Concurrent anti-retroviral therapy that would inactivate the investigational agent.
14. Pre-menopausal or non-surgically sterile women who are unwilling to use an effective form of contraception such as the contraceptive pill or intrauterine device.
15. Pregnant or breastfeeding women.
16. Males or females who do not agree to use barrier contraception as specified in the inclusion criteria.
17. History of any investigational agent within 28 days prior to UshStat administration.
18. Participation in a prior gene transfer therapy study.
19. Enrolment in any other clinical study, for any condition, including those relating to Usher syndrome type 1B, throughout the duration of the UshStat study.
20. Current or anticipated treatment with anticoagulant therapy or the use of anticoagulation therapy within the four weeks prior to surgery.
21. Long-term treatment with systemic corticosteroids within 28 days prior to the screening visit or ongoing systemic corticosteroid treatment at screening or on Day -1.
22. Current treatment with immunosuppressant therapies.
23. A history of malignancy within a five year period or have had a positive cancer screening test within a one year period of the screening visit.
24. Past medical history of HIV, or hepatitis A, B or C.
25. Inability to comply with the study protocol.

5.0 ENDPOINTS

5.1 Primary Endpoints

The primary objective of this study is evaluation of safety and tolerability of ascending doses of UshStat in patients with Usher syndrome type 1B. Safety and tolerability of the IMP will be evaluated using the following endpoints:

- The incidence of AEs over a 12-month period following a single intraocular dose of UshStat.
- Clinically important changes from baseline (Day -28) in the following safety assessments:
    - Best-corrected visual acuity (BCVA)
    - Slit-lamp examination
    - Indirect ophthalmoscopy
    - Fundus photography
    - Intraocular pressure (IOP)
    - Ocular coherence tomography (OCT)
    - Laboratory parameters
    - Vital signs
    - Concomitant medications
    - Physical examinations

For all primary endpoints with repeated measures, the primary time point will be considered the Week 48 (12-month) visit unless otherwise specified. BCVA and perimetry measurements are subject to broad intra-individual variability therefore the baseline value used for these measures will be an average of all the values obtained during the screening period.

5.2 Secondary Endpoints

The secondary objective is to evaluate UshStat for possible biological activity. An attempt will be made to determine a delay in retinal degeneration following subretinal injection of UshStat, through changes in function relative to the untreated contralateral eye using the following retinal analytical techniques:

- BCVA
- Indirect ophthalmoscopy
- Visual function questionnaire (VFQ-25)
- Full dilated slit-lamp examination
- Fundus photography – photomontage
- Visual field testing: Semi-automated Kinetic Perimetry (SKP), Full-Field GATE Static Perimetry, and microperimetry
- Autofluorescence

- Electroretinogram (ERG)
- OCT

The primary time points for secondary endpoints will be considered the Week 24 (6-month) and Week 48 (12-month) visits.

5.3 Other Endpoints

5.3.1 Immunology Endpoint

Humoral antibody response to UshStat administration.

5.3.2 Clinical Laboratory Tests

Hematology, biochemistry, urinalysis and other laboratory data will be measured at various time points throughout the study. 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 adverse events. 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.

5.3.3 Biodistribution Endpoint

UshStat distribution in blood and urine will be assessed by polymerase chain reaction (PCR).

6.0 GENERAL STATISTICAL CONSIDERATIONS

6.1 Sample Size

This is an exploratory study for which the primary objective is to evaluate safety through adverse events and clinically meaningful impacts on vision endpoints. No formal sample size calculation has been performed. A total of 18 patients will be enrolled in five cohorts. The first three cohorts will consist of three patients each, and three and six patients will be enrolled in the fourth and fifth cohorts, respectively, at the MTD.

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 study protocol. If a patient withdraws from the study, the Week 48 procedures will be completed where possible.

6.3 Handling Data Irregularities

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 data collected 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 individuals are unable to provide reliable results (e.g., poor fixation 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 prior to dose escalation, but the following section provides analyses that are specific to DSMB reports.

Following completion of Part B of the study, an interim review of data will be conducted on all available safety data and any available preliminary efficacy/activity data up to the three-month time point for patients in the first four cohorts. This review, consisting of descriptive statistics and exploratory figures will be used to provide data to the FDA and IRB/ethics committees before pediatric patients are enrolled in Cohort 5. Formal statistical tests will not be performed as part of the analysis.

6.5 Analyses Specific to DSMB Reports

At a minimum, the DSMB will be provided with the following accumulating data prior to making decisions regarding dose escalation:

- Adverse events and concomitant medications
- Laboratory results
- Humoral antibody response and vector distribution data
- BCVA
- IOP
- Slit lamp examination and fundoscopy data

Note that additional endpoint 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 presented upon final analyses, and at a minimum, those relevant to the above endpoints 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.

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 UshStat 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 Investigational Product. The following sections describe data presentations which will be available for review prior to proceeding to each cohort and/or at the end of the study. Some variables (primarily ophthalmic variables) may be combined with others in patient profiles. 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 UshStat, but all results contributing to the primary and secondary endpoints and assessments of safety at all study visits will be presented.

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 height, weight, vital signs, 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.

7.3 Primary Endpoint

The primary endpoint is composed of several endpoints 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 endpoints, except adverse events, will compare change from Day -28 to Week 48. Graphical presentation of cohort summaries will also be presented as described, and clinically important changes from Baseline (Day -28) to Week 48 will be indicated and summarized.

7.3.1 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), 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 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 AE (death)
- At least one serious AE
- At least one severe AE
- At least one AE related to IMP
- At least one TEAE related to procedure
- Without any AEs

In addition, tables will present both the number and percentage of TEAEs and patients with TEAEs by SOC, HLT, PT, severity and cohort. Adverse events of special interest (AESI), detailed in the protocol, will be summarized by SOC, HLT, PT, severity and cohort. AESIs 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 AE 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 oedema
- Subretinal fluid
- Uveitis
- Vitreous floaters

7.3.2 Best-Corrected Visual Acuity (BCVA)

BCVA (Early Treatment Diabetic Retinopathy Study [ETDRS] letters read) will be listed by visit and eye. BCVA for all patients' study eye and fellow eye will be presented graphically by visit and cohort. Mean changes in BCVA by visit and cohort will be summarized in a table and graph 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 similar to the other ophthalmic endpoints. Summary counts for the number of 'step-up' and 'step-down' changes in the inflammation scale in the study eye may be tabulated by cohort and visit. Clinically important changes (i.e., $\geq$ 2 step change) as observed in slit lamp examination and/or indirect ophthalmoscopy at any point from Day -28 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. IOP will be listed by visit and eye. IOP for all patients' study eye and fellow eye will be presented graphically by visit and cohort. Mean changes in IOP by visit and cohort will be summarized in a table and graph by cohort and visit.

Clinically important changes and the number of individuals with IOP $\geq$ 25, $\geq$ 30, and $\geq$ 35 mmHg at any point from Day -28 to Week 48 will be tabulated by cohort and visit.

7.3.5 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 the other ophthalmic endpoints. 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.

7.3.6 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, lactate dehydrogenase), kidney and liver function tests (creatinine, blood urea nitrogen, uric acid, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, total protein, albumin, gamma glutamic transpeptidase, cholesterol), coagulation (prothrombin time and partial thromboplastin time) urinalysis (color, appearance, specific gravity, pH, protein, glucose, ketones, blood, bilirubin, microscopy), and urine pregnancy test (for females of childbearing age) 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 graded by site physicians, and clinically significant abnormal lab values will also be recorded as AEs.

7.3.7 Vital Signs

Vital signs will be summarized and also 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 or clinically significant changes in patients' vital signs will be indicated.

7.3.8 Concomitant Medications

Concomitant medications including the WHO drug coding will be listed by patient, cohort and study visit.

7.3.9 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. Clinically significant changes, occurring if an assessment was normal at Day -28 but is abnormal at Week 48, in physical examination assessments from Day -28 to Week 48 will be indicated.

7.4 Secondary Endpoints

The secondary endpoints include changes in the study eye from Day -28 to Weeks 24 and 48 in function relative to the untreated, contralateral eye in several visual function measures. The primary endpoints of BCVA, ocular inflammation and OCT will also serve as secondary endpoint measures. Analysis of these parameters will be conducted as outlined in Sections 7.3.2, 7.3.3 and 7.3.5, respectively.

7.4.1 Full-field Kinetic and Static Perimetry

Full-field kinetic and static perimetry will be used to document scotoma and the level of retinal function for each patient, and clinically significant changes from Day -28 will be highlighted. Perimetry will be performed three times during the screening period (once at Day -28 and twice at Day -1) and the mean of the reported perimetry values will be used to determine baseline perimetry measurements.

Individual and mean change in 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 by patient, cohort and visit.

Semi-automated kinetic perimetry (SKP) will be used to estimate total area (degrees^2) of visual field sensitivity for different stimulus intensity levels (I4e, III4e and V4e isopters). Individual and mean change in total areas will be plotted against time. Values in each eye will be listed by patient, cohort and visit.

7.4.2 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 for study eye and fellow eye as appropriate. Mean changes from baseline will also be summarized. Clinically significant changes, defined as a decrease in ERG amplitude of greater than 50%, from Day -28 ERG data will be indicated and listed where appropriate.

Peak amplitudes (nV/deg^2) and latency (ms) values for multifocal ERG (mfERG) responses at Day -28 will be tabulated for each of six concentric rings in the visual field by patient and eye. The concentric ring minimum and maximum are collected separately. The minimum and maximum are summed together to obtain the peak amplitude (nV/deg^2). To examine change

in mfERG responses in the central visual field across visits, the mean changes from Day -28 across the peak amplitudes and latencies of inner rings (Rings 1-3) will be tabulated and plotted against time by cohort, patient and eye. In addition, mean changes across the peak amplitude and latencies of outer rings (Rings 4-6) will also be tabulated and plotted by cohort, patient and eye against time.

7.4.3 Visual Function Questionnaire (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 Day -1 to Week 48 will be tabulated by patient and cohort and 95% confidence limits and/or ranges will be provided. Meaningful changes from Day -1 will be highlighted where appropriate.

7.4.4 Supplementary Reading Center Data

Fundus photography photomontage, fundus autofluorescence (FAF), and microperimety data will all be analyzed separately by Translational Clinical Trials Center (TCTC) at Casey Eye Institute, the Central Reading Center at the end of the study. These exploratory measures will not be summarized for DSMB meetings.

7.5 Other Endpoints

7.5.1 Immunology

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

7.5.2 Biodistribution Endpoint

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

7.6 Safety Analysis

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

7.6.1 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/FIGURES

This section contains a list of proposed tables and figures that will be presented in analysis of study data, but not all figures and tables will be included in DSMB reports. At a minimum, figures and tables from Sections 8.1 through 8.4.2 will be included in DSMB reports, but additional figures and tables from remaining sections will be included when possible.

8.1 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.

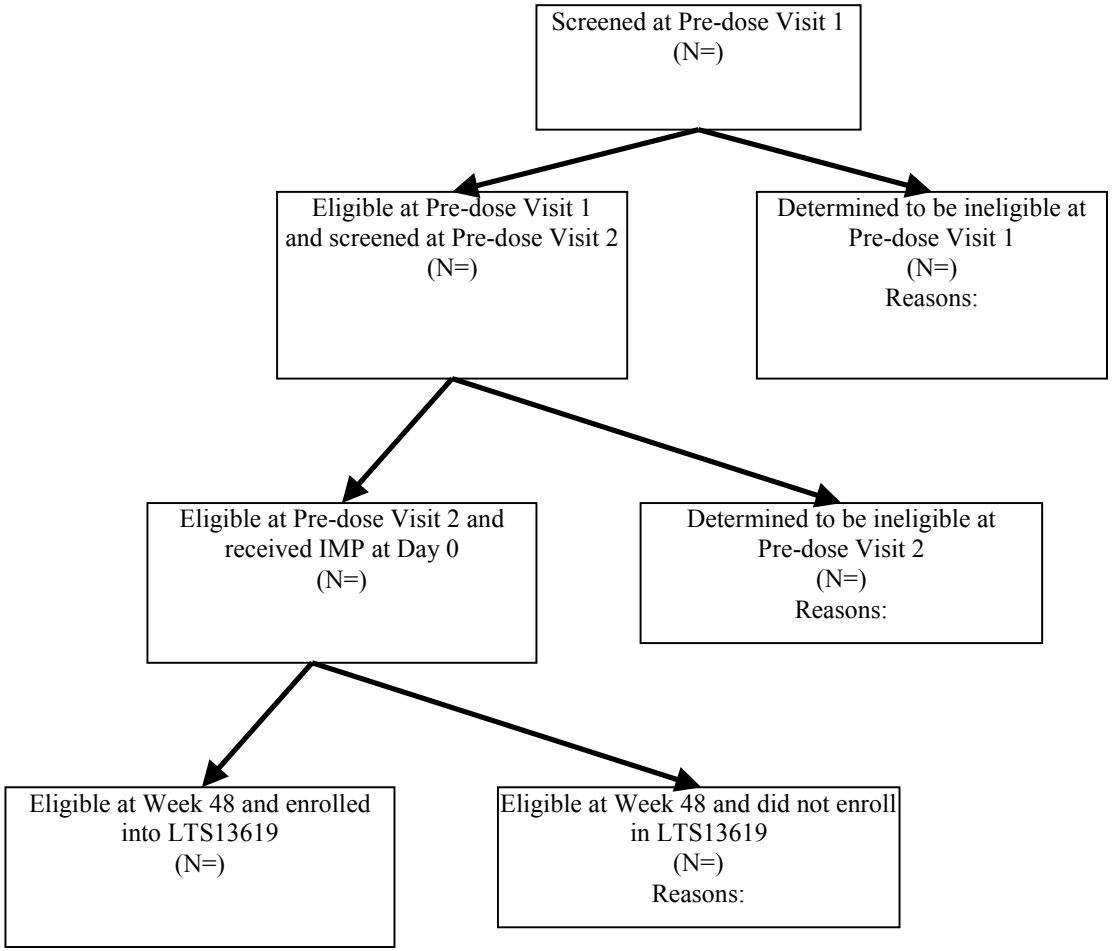


Table 1C will list the overall numbers and percentages of patients completing and withdrawing from the study, and these values will also be stratified by cohort. Reasons for withdrawal, including death will be provided where applicable.

Table 1C: Study Follow-up Completion and Withdrawal (including deaths)

Cohort	Completed N (%)	Withdrawals N (%)
1		
2		
3		
4		
5		
Total		

8.2 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 (N=X)	Cohort 2 (N=X)	Cohort 3 (N=X)	Cohort 4 (N=X)	Cohort 5 (N=X)
AGE (years)	Median (Range)	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 (%)
	Male	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
RACE	American Indian or Alaskan Native	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Asian	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Black or African American	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Native Hawaiian or other Pacific Islander	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Other	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	White	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
ETHNICITY	Hispanic or Latino	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Not Hispanic or Latino	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)
WEIGHT (kg)	Median (Range)	X (X-X)	X (X-X)	X (X-X)	X (X-X)	X (X-X)	X (X-X)

Table 2B will list demographic information by patient.

Table 2B: Detailed Demographic Listing by Cohort

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

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

Table 2C: 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

Table 2D 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. See Section 9 for patient profile examples.

Table 2D: Baseline Physical Examination Parameters by Cohort

		All Eligible Patients	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5
Cardiovascular Assessments	Normal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Abnormal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Dermatologic Assessments	Normal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Abnormal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Endocrine/Metabolic Assessments	Normal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Abnormal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
GI Assessments	Normal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Abnormal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Genitourinary Assessments	Normal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Abnormal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Head/ENT Assessments	Normal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Abnormal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Lymphatic/Hematologic Assessments	Normal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Abnormal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Musculoskeletal Assessments	Normal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Abnormal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Neurologic Assessments	Normal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Abnormal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

		All Eligible Patients	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5
Psychologic Assessments	Normal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Abnormal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Respiratory Assessments	Normal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Abnormal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

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

Table 2E: Reproductive Status by Patient

Patient ID	Hysterectomy	Vasectomy	Tubal ligation	Postmenopausal	Other

Patient profiles will provide notable ocular history at baseline for each patient in tabular format. Please refer to Section 9 for examples of patient profiles.

8.3 Primary Outcome Analyses

8.3.1 Adverse Events

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

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

	Patients						Events					
	All	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	All	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5
Type of Event												
Fatal	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
No Events	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Related to IMP	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Related to Procedure	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Serious	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Severe	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

Table 3B: Number of TEAEs by MedDRA SOC, HLT, PT, Severity and Cohort (Event-based Counts)

			COHORT											
			1	2			3			4		All Cohorts		
			Mild	Mild	Moderate	Mild	Moderate	Severe	Mild	Moderate	Mild	Moderate	Severe
SYSTEM ORGAN CLASS (SOC)	HIGH LEVEL TERM (HLT)	PREFERRED TERM (PT)											
SOC1	HLT1	PT1											
		PT2											
SOC2	HLT1												
		PT1											
		PT2											
All													

Table 3C: Number of Patients Experiencing TEAEs by MedDRA SOC, HLT, PT, Severity and Cohort (Patient-based Counts)

(Note that if more than one event in each category is reported for a single patient, the most recent event of maximum severity is counted.)

			COHORT											
			1	2			3			4		All Cohorts		
			Mild	Mild	Moderate	Mild	Moderate	Severe	Mild	Moderate	Mild	Moderate	Severe
SYSTEM ORGAN CLASS (SOC)	HIGH LEVEL TERM (HLT)	PREFERRED TERM (PT)											
SOC1	HLT1	PT1											
		PT2											
SOC2	HLT1												
		PT1											
		PT2											
All													

Table 3D: Number of TEAEs of Special Interest by MedDRA SOC, HLT, PT, Severity and Cohort (Event-based Counts)

			COHORT											
			1	2			3			4		All Cohorts		
			Mild	Mild	Moderate	Mild	Moderate	Severe	Mild	Moderate	Mild	Moderate	Severe
SYSTEM ORGAN CLASS (SOC)	HIGH LEVEL TERM (HLT)	PREFERRED TERM (PT)											
SOC1	HLT1	PT1											
		PT2											
	HLT1												
		PT1											
		PT2											
All\													

Tables 3E and 3F summarize TEAEs and patients with at least one TEAE by MedDRA SOC, HLT, PT, severity and cohort, with all inflammatory events grouped into a single PT.

Table 3E: Number of TEAEs by MedDRA SOC, HLT, PT, Severity and Cohort with Inflammatory Events Grouped (Event-based Counts)

			COHORT											
			1	2			3			4		All Cohorts		
			Mild	Mild	Moderate	Mild	Moderate	Severe	Mild	Moderate	Mild	Moderate	Severe
SYSTEM ORGAN CLASS (SOC)	HIGH LEVEL TERM (HLT)	PREFERRED TERM (PT)											
SOC1	HLT1	PT1											
		PT2											

			COHORT											
			1		2		3		4		All Cohorts			
			Mild	Mild	Moderate	Mild	Moderate	Severe	Mild	Moderate	Mild	Moderate	Severe	
SOC2	HLT1													
		PT1												
		PT2												
All														

Table 3F: Number of Patients Experiencing TEAEs by MedDRA SOC, HLT, PT, Severity and Cohort with Inflammatory Events Grouped (Patient-based Counts)

(Note that if more than one event in each category is reported for a single patient, the most recent event of maximum severity is counted.)

			COHORT											
			1		2		3		4		All Cohorts			
			Mild	Mild	Moderate	Mild	Moderate	Severe	Mild	Moderate	Mild	Moderate	Severe	
SYSTEM ORGAN CLASS (SOC)	HIGH LEVEL TERM (HLT)	PREFERRED TERM (PT)												
SOC1	HLT1	PT1												
		PT2												
SOC2	HLT1													
		PT1												
		PT2												
All														

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

Table 3G: Number of TEAEs Related to IMP by MedDRA SOC, HLT, PT, Severity and Cohort (Patient-based Counts)

			COHORT										
			1	2		3			4		All Cohorts		
			Mild	Mild	Moderate	Mild	Moderate	Severe	Mild	Moderate	Mild	Moderate	Severe
SYSTEM ORGAN CLASS (SOC)	HIGH LEVEL TERM (HLT)	PREFERRED TERM (PT)											
SOC1	HLT1	PT1											
		PT2											
SOC2	HLT1												
		PT1											
		PT2											
All													

Table 3H: Number of TEAEs Related to Procedure by MedDRA SOC, HLT, PT, Severity and Cohort (Patient-based Counts)

			COHORT										
			1	2		3			4		All Cohorts		
			Mild	Mild	Moderate	Mild	Moderate	Severe	Mild	Moderate	Mild	Moderate	Severe
SYSTEM ORGAN CLASS (SOC)	HIGH LEVEL TERM (HLT)	PREFERRED TERM (PT)											
SOC1	HLT1	PT1											
		PT2											

			COHORT									
			1	2		3			4	All Cohorts		
			Mild	Mild	Moderate	Mild	Moderate	Severe	Mild	Moderate	Mild	Moderate	Severe
SOC2	HLT1											
		PT1										
		PT2										
All												

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

Table 3I: 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 3J: Listing of TEAEs by Patient and Cohort

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

								Relatedness		MedDRA Classification		
Cohort	Patient ID	Surgery Date	AE Description	Event Date	Outcome	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 Adverse Events of Special Interest by Patient and Cohort

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

8.3.2 BCVA, Ocular Inflammation and IOP

Table 3L lists the primary outcomes of BCVA, ocular inflammation and IOP for the study and fellow eyes by patient and visit, Tables 3M and 3N summarize mean changes in BCVA and IOP, respectively, by cohort and visit for the study and fellow eyes and Table 3O summarizes the number and percentage of individuals with elevated (≥ 25, ≥ 30 and ≥ 35 mmHg) IOP in the study eye. Changes in ophthalmic inflammation by dose group, visit and eye will also be summarized in Table 3P. Ophthalmic outcome data will be displayed graphically in plots similar to Figures 3Q and 3R. Tables and plots will be given for the study eye as well as for the fellow eye, and labeled appropriately.

Table 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: 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**										

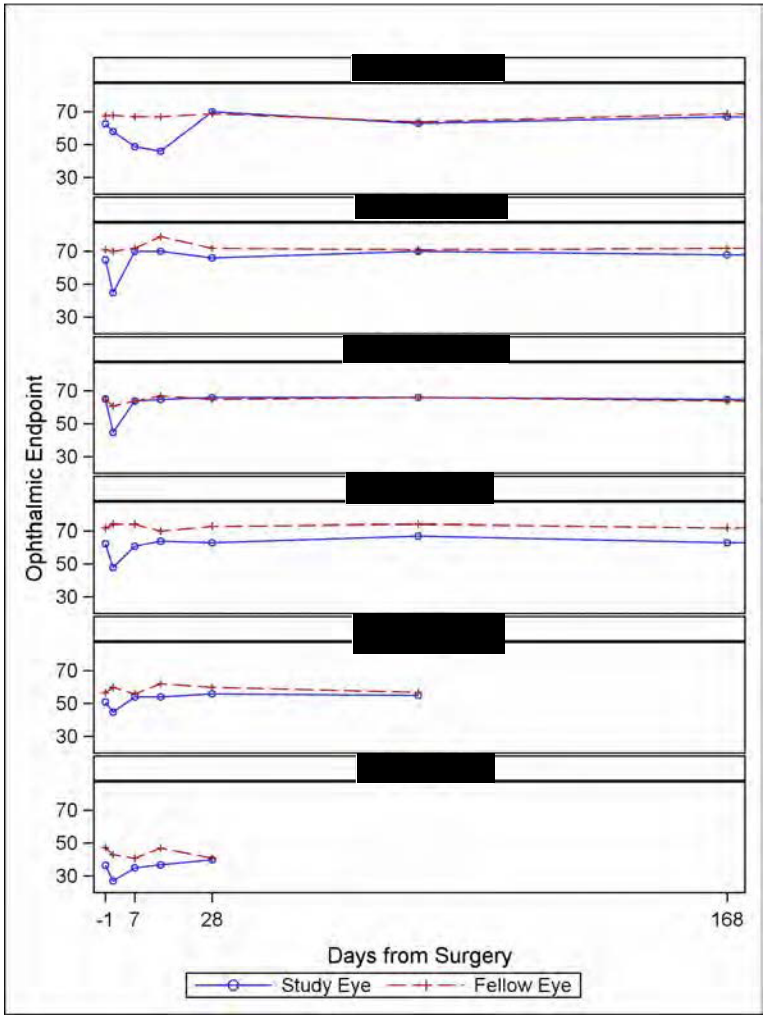
Table 3O: Patients Experiencing Elevated IOP in the Study Eye Following Treatment by Cohort

	IOP >= 25 mmHg				IOP >= 30 mmHg				IOP >= 35 mmHg			
	No		Yes		No		Yes		No		Yes	
	N	%	N	%	N	%	N	%	N	%	N	%
Cohort												
1												
2												
3												
4												
5												
All												

Table 3P: Changes in Ophthalmic Inflammation in the Study Eye by Cohort and Visit

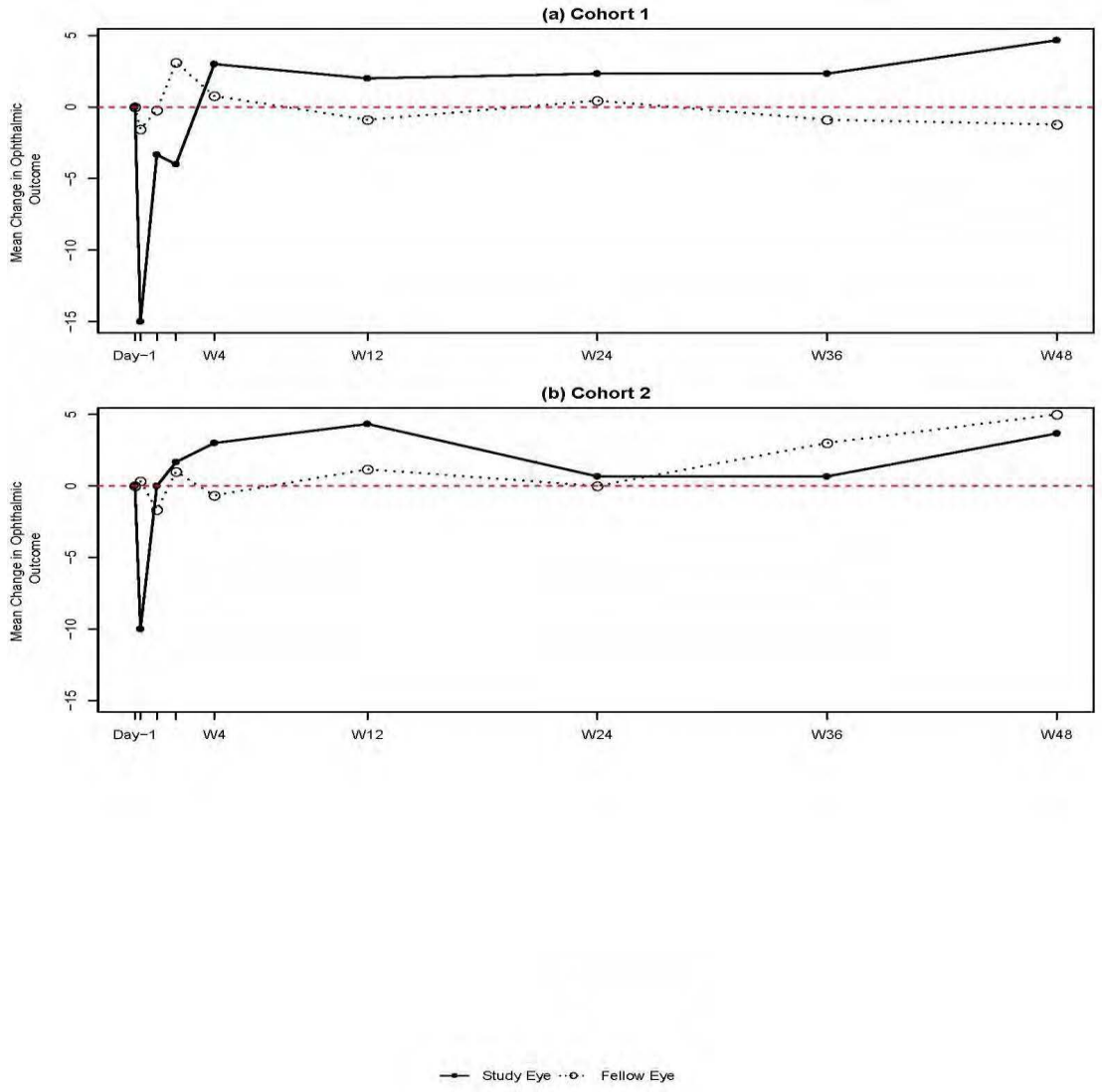
		Anterior Chamber Cells				Anterior Chamber Flare				Vitreous Cells						Vitreous Haze					
		No Change		Half-Step Increase		No Change		1-Step Increase		Half-Step Decrease		No Change		Half-Step Increase		2-Step Decrease		1-Step Decrease		No Change		Half-Step Increase	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%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

Figure 3Q: Ophthalmic Outcomes Over Time (Days from Surgery) by Patient



Mean changes from Baseline (Day -28) will be plotted for ophthalmic outcomes versus dose cohort in a plot similar to Figure 3R.

Figure 3R: Mean Change in Ophthalmic Outcome from Baseline by Dose Cohort



8.3.3 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. Table 3S lists the patients that had abnormal and/or clinically significant lab values.

Table 3S: 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.**

Table 3T summarizes mean changes from Baseline for each continuous laboratory parameter.

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

							Quartiles			95% CI	
Lab Category	Lab Name	Cohort	Visit	N	Mean	Std	25%	50%	75%	Lower	Upper

8.3.4 OCT

Table 3U lists OCT data by patient. This information will also be included in patient profiles. See Section 9 for patient profile examples. Figures similar to 3Q and 3R may also be used to summarize continuous OCT endpoint variables.

Table 3U: OCT Listing by Patient and Visit

		Central Macular Thickness		Macular Volume		Increase in Cystoid Macualr Edema		Unfavorable Change in Subretinal Fluid			Comments	
Patient ID	Visit	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	OCT Data	Study	Fellow

8.3.5 Vital Signs

Table 3V summarizes median vital signs by cohort and visit. A listing of vital signs by visit will be provided in each patient's profile report (see Section 9). Clinically significant changes or abnormalities will be noted.

Table 3V: Vital Signs

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

8.4 Secondary Outcome Analyses

8.4.1 Full-field Kinetic and Static Perimetry

Individual and mean static perimetry data will be presented similarly to other ophthalmic outcome data as in Figures 3L and 3M. Individual scotoma as measured by kinetic perimetry may be represented graphically where appropriate in a patient profile. Tables 4A and 4B list static (GATE) and kinetic (SKP) data, respectively, by cohort, patient and visit for both study and fellow eyes.

Table 4A: Static (GATE) Perimetry Data by Patient

Cohort	Patient ID	Visit	Volume of Full Field Hill of Vision (Decibel Steradians)		111pt grid- Volume of Full Field Hill of Vision (Decibel Steradians)	
			Study	Fellow	Study	Fellow

Table 4B: Kinetic (SKP) Perimetry Data by Patient

Cohort	Patient ID	Visit	I4E Isopter Area (Squared Degrees)		III4E Isopter Area (Squared Degrees)		V4E Isopter Area (Squared Degrees)		VI4E Isopter Area (Squared Degrees)	
			Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow

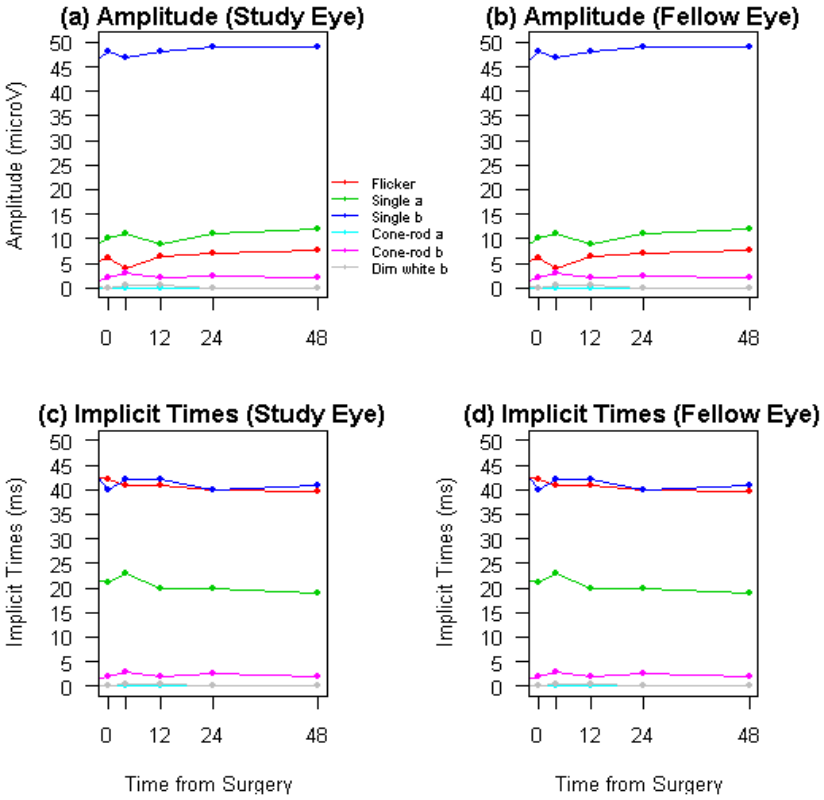
8.4.2 ERG

Table 4C lists full field ERG response amplitudes (microvolts) and implicit times (ms) parameters by patient and visit for the study eye. Fellow eye data will be summarized similarly. The a- and b- wave amplitudes and implicit times may be represented graphically, similar to Figure 4D by patient and cohort as appropriate. Mean change in full field ERG will also be summarized. Clinically significant changes from Day -28 in ERG data will be indicated and listed where appropriate.

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

Cohort	Patient ID	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)		Comments
			Amplitude	Implicit Time	Amplitude	Implicit Time	Amplitude	Implicit Time	Amplitude	Implicit Time	Amplitude	Implicit Time	Amplitude	Implicit Time	

Figure 4D: Full Field ERG Data Over Time



Tables 4E, 4F and 4G list the mean peak amplitude and latencies for each patient at Day -28 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. Figures 4H and 4I illustrate the change in peak and latency values for the central and peripheral visual fields, respectively, against time for each patient.

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

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

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

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

Figure 4H: Change in Central Field (Rings 1-3) mfERG Response Over Time

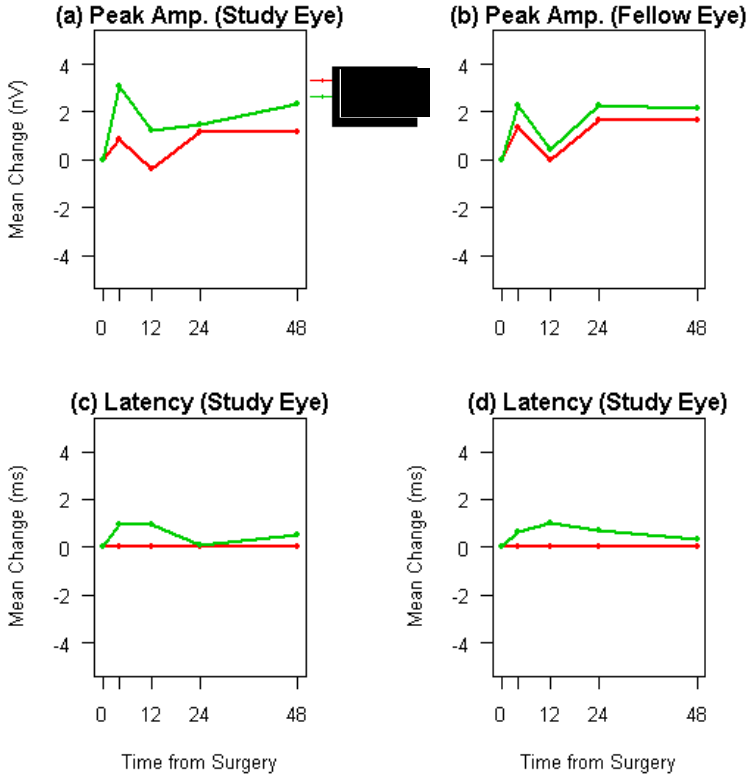
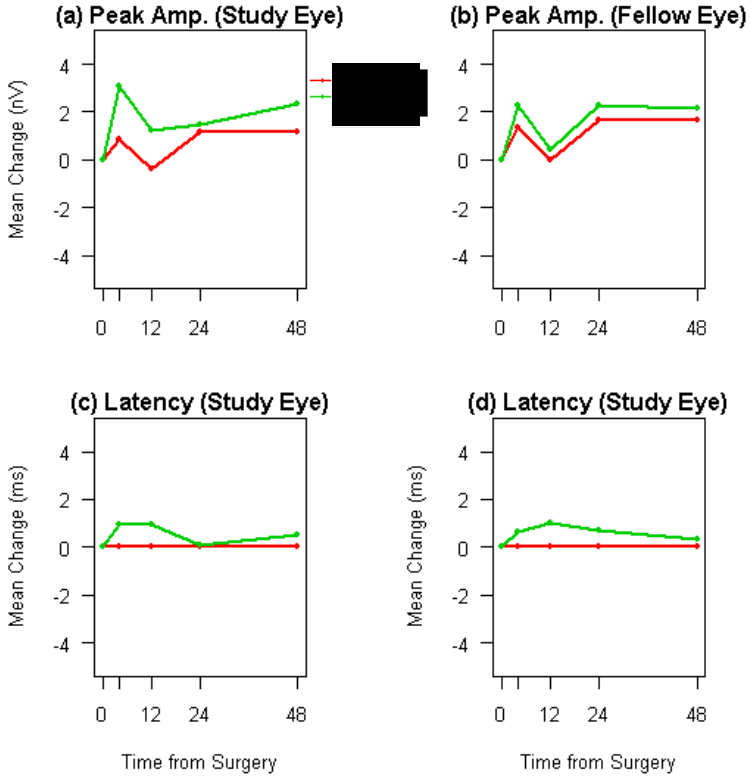


Figure 4I: Change in Peripheral Field (Rings 4-6) mfERG Response Over Time



8.4.3 VFQ-25

At the end of the study, mean change in VFQ-25 scores will be tabulated by cohort (Table 4J) and may be summarized using plots similar to those in Figures 3L and 3M. Please refer to Section 8.3.2 for these plots.

Table 4J: Change in VFQ-25 by Cohort

Cohort	Mean (SD) Change VFQ-25	95% Confidence Limits

8.5 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.

8.5.1 Immunology

Table 5A: Detailed Listing of Immunologic Results 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			

8.5.2 Biodistribution Endpoint

Table 5B: 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										

9.0 PATIENT PROFILES

An overall summary will be provided for each patient so that safety may be evaluated by case. The following sections contain a list of proposed tables and plots summarizing data from TDU13600 and LTS13619 that are included in each patient profile.

9.1 Baseline Characteristics

DEMOGRAPHY											
Patient ID	Cohort	Date of birth	Age	Gender	Race	Ethnicity	Study Eye	Screening Date	Surgery Date	Termination Date	Mutation
COMMENTS:											

OCULAR MEDICAL HISTORY		
Condition	**Study Eye**	**Diagnosis Date**
COMMENTS:		

MEDICAL HISTORY		
Disease/Disorder	**Date of Diagnosis**	**Ongoing**
COMMENTS:		

PRIMARY ENDPOINTS (ADVERSE EVENTS)										
AE Description	**Start Date (Study Day)**	**End Date Ongoing**	**Outcome**	**Severity**	**AESI**	**SAE**	**Related to Surgery**	**Related to Investigation Medicinal Product**	**System Organ Class**	**Preferred Term**
COMMENTS:										

STUDY EYE EXAMINATION (ABNORMALITIES)								
Visit	**Macular Edema**	**Abnormal Optic Nerve**	**Retinal Detachment**	**Intraretinal Hemorrhage**	**Subretinal Hemorrhage**	**Subretinal Fibrosis**	**Other**	**Specify Other**
COMMENTS:								

IMMUNOLOGY					
Visit	ELISA Assay Result-Baseline	ELISA Assay Result-Post Admin	Positive/Negative ELISA Response	Western Blot Required	Positive/Negative Western Blot Result

BIODISTRIBUTION										
Specimen	Screening	Day 0	Day 1	Week 1	Week 2	Week 4	Week 12	Week 24	Week 36	Week 48
COMMENTS:										

IOP, BCVA, OCULAR INFLAMMATION[1]															
		BCVA		IOP		Anterior Cells		Anterior Flare		Vitreous Cells		Vitreous Haze		Macular Edema	
Visit	Visit Date	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow
COMMENTS:															

[1]The SC1 BCVA is not presented in the table because the SC2 BCVA is an average of the SC1 and SC2 BCVA values.

OCT													
	Central Macular Thickness		Macular Volume		Evidence of Treatment Efficacy		Increase inCystoid MacularEdema		Unfavorable Changein SubretinalFluid		Reported AE		
Visit	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	OCT Data

OCT													
	Central Macular Thickness		Macular Volume		Evidence of Treatment Efficacy		Increase inCystoid MacularEdema		Unfavorable Changein SubretinalFluid		Reported AE		
Visit	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	OCT Data
COMMENTS:													

PERIMETRY												
	Static (GATE) Perimetry				Kinetic (SKP) Perimetry							
	Volume of Full Field Hill of Vision (Decibel Steradians)		111 pt grid-Volume of Full Field Hill of Vision (Decibel Steradians)		I4E Isopter Area (Squared Degrees)		III4E Isopter Area (Squared Degrees)		V4E Isopter Area (Squared Degrees)		VI4E Isopter Area (Squared Degrees)	
Visit	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow
COMMENTS:												

FULL-FIELD ERG RESPONSE													
	Light adapted 3.0 flicker ERG		Light adapted 3.0 ERG a-wave		Light adapted 3.0 ERG b-wave		Dark adapted 3.0 ERG a-wave		Dark adapted 3.0 ERG b-wave		Dark adapted 0.01 ERG b-wave		
Visit	Amp	Imp Time	Amp	Imp Time	Amp	Imp Time	Amp	Imp Time	Amp	Imp Time	Amp	Imp Time	Comments
COMMENTS:													

MEAN PEAK AMPLITUDES AND LATENCIES AT BASELINE (mfERG)														
	Amplitude (nV/deg^2) - max+min Latency (ms)													
	Ring 1		Ring 2		Ring 3		Ring 4		Ring 5		Ring 6		Comments	
Visit	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow

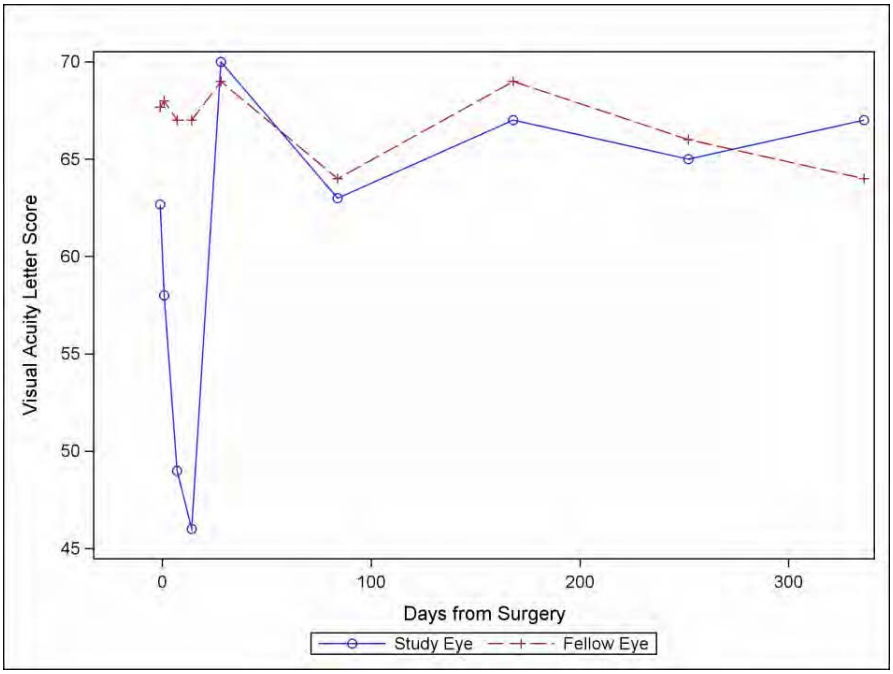
MEAN PEAK AMPLITUDES AND LATENCIES AT BASELINE (mfERG)														
	Amplitude (nV/deg^2) - max+min Latency (ms)													
	Ring 1		Ring 2		Ring 3		Ring 4		Ring 5		Ring 6		Comments	
Visit	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow
COMMENTS:														

COMMENTS

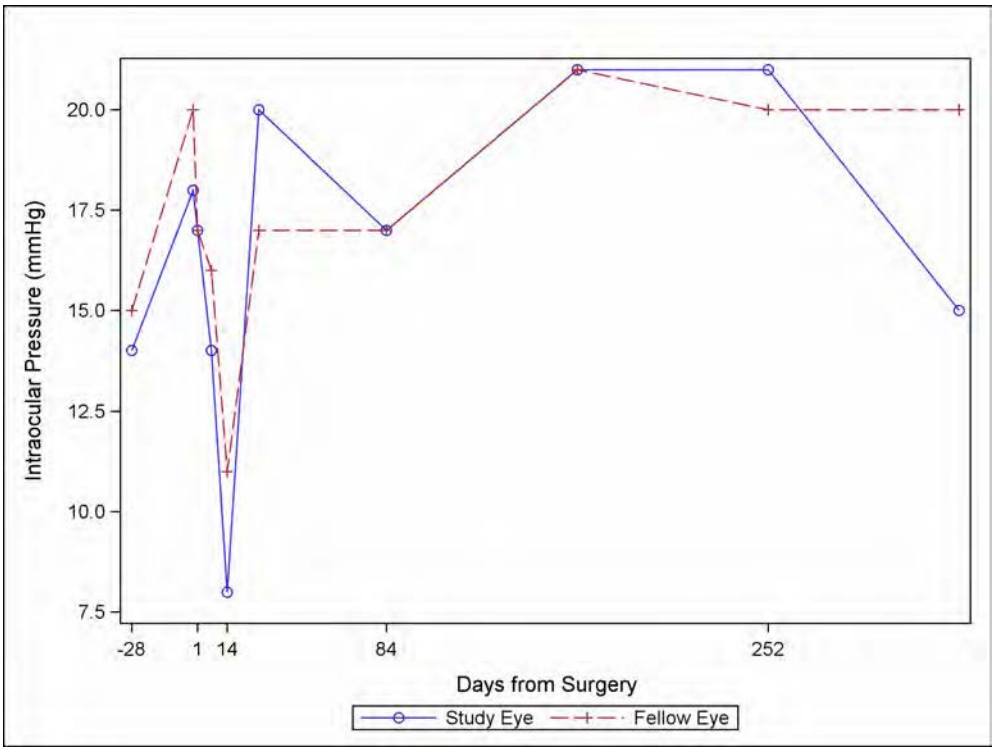
SUMMARY CLINICAL OBSERVATIONS

OVERALL CONCLUSIONS

Visual Acuity



Intraocular Pressure (IOP)



ADMINISTRATION OF INVESTIGATIONAL PRODUCT					
Surgery Date	Full Dose Administered	Fluid-air Exchange Performed	Air Bubble Removed	Procedure Resulted in Retinal Tear	Complication(s) During Surgery
COMMENTS:					

	ECG			CHEST X-RAY		
Visit	Abnormal	CS	Specify	Abnormal	CS	Specify
COMMENTS:						

VITAL SIGNS					
			Blood Pressure		
Visit	Temperature (°F)	Respiratory Rate (/min)	Systolic	Diastolic	Pulse (/min)
COMMENTS:					

PHYSICAL EXAM												
	Cardiovascular		Dermatologic		Endocrine/Metabolic		Gastrointestinal		Genitourinary		Head/ENT	
Visit	Abnormalities	Change from Baseline	Abnormalities	Change from Baseline	Abnormalities	Change from Baseline	Abnormalities	Change from Baseline	Abnormalities	Change from Baseline	Abnormalities	Change from Baseline
COMMENTS:												

PHYSICAL EXAM										
	Lymphatic/Hematologic		Musculoskeletal		Neurologic		Psychologic		Respiratory	
Visit	Abnormalities	Change from Baseline	Abnormalities	Change from Baseline	Abnormalities	Change from Baseline	Abnormalities	Change from Baseline	Abnormalities	Change from Baseline
COMMENTS:										

LENS ASSESSMENT										
		Natural Lens		Nuclear Score		Cortical Score		PCS Score	
Visit	Visit Date	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow
COMMENTS:									

FUNDUS PHOTOS TDU Study												
	Treatment Efficacy		Increased Inflammation		Hemmorhage		Reported AE		Retinal Detachment		Comments	
Visit	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow	Study	Fellow
COMMENTS:												

NOTE: For Laboratory Listings, Yellow Indicates Outside of Site's Normal Laboratory Reference Range

HEMATOLOGY[2,3]										
Visit	WBC (10^9/L)	RBC (10^{12}/L)	Haemoglobin (g/L)	Haematocrit	MCV (fL)	MCH (pg/cell)	RDW	Platelets (10^9/L)	Neutrophils	Neutrophils Total (10^9/L)
COMMENTS:										

HEMATOLOGY[2,3]			
Lymphocytes	Monocytes	Eosinophils	Basophils
COMMENTS:			

[2]Neutrophil totals were not collected until September 2014
[3]RDW-CV values were converted from RDW-SD values

	COAGULATION		CHEMISTRY									
Visit	PT (seconds)	PTT (seconds)	Phosophorus (mmol/L)	Calcium (mmol/L)	Sodium (mEq/L)	Chloride (mEq/L)	Bicarbonate (mEq/L)	Potassium (mEq/L)	Fasting Blood Glucose (mmol/L)	Blood Glucose (mmol/L)	Creatinine kinase (umol/L)	Lactate Dehydrogenase (U/L)
COMMENTS:												

	KIDNEY AND LIVER FUNCTION										
	Kidney Function			Liver Function							
Visit	Creatinine (umol/L)	BUN (mmol/L)	Uric Acid (umol/L)	ALT (U/L)	AST (U/L)	Total Bilirubin (umol/L)	Alkaline Phosphatase (U/L)	Total Protein (g/L)	Albumin (g/L)	GGT (U/L)	Cholesterol (mmol/L)
COMMENTS:											

URINALYSIS				
Visit	**Protein (Negative)**	**Blood (Negative)**	**Ketones (Negative)**	**Urine Pregnancy Test (Negative)**
COMMENTS:				

CONCOMITANT MEDICATIONS									
Start Date	**Action Date**	**Action**	**Medication Name**	**Indication**	**Route**	**Dose**	**Units**	**Schedule**	**Result of AE**
COMMENTS:									

SANOFI

SAR421869 TDU13600
COORDINATING CENTER

August 30, 2019

Subject: **Table of Contents for Final Tables, Listings and Figures (TLFs)** – SAR421869 Protocol TDU13600

The purpose of this memorandum is to document that the Table of Contents for the final analysis for TDU13600 will differ from the Table of Contents in the currently approved version 2 of the SAP, dated 22JUL2016. The format of the tables will be the same as those in the SAP, except that the adverse event tables will be updated to the format used for the 23MAY2018 DSMB Report for SAR422459. The TOC and the adverse event table shells to be used for the final TLFs are included below.

Coordinating Center Statistician Signature: [redacted] Date: 30AUG2019

Sponsor Statistician Signature: Date: 04Sep2019

Coordinating Center Director Signature: Date: 24SEP2019

TOC FOR ALL TLFS FOR TDU13600

- Table 3O: Patients Experiencing BCVA Change in the Study Eye at Week 48 Following Treatment by Cohort
- Table 3P: Patients Experiencing Elevated IOP in the Study Eye at Week 48 Following Treatment by Cohort
- Tables 3Q-3S: Changes in Ophthalmic Inflammation in the Study Eye by Cohort and Visit
- Figures 3T-3V: BCVA in Study and Fellow Eyes by Patient in Cohort X
- Figures 3W-3Y: IOP in Study and Fellow Eyes by Patient in Cohort X
- Figure 3Z: Mean Changes in BCVA in the Study Eye over Time by Cohort
- Figure 3AA: Mean Changes in IOP in the Study Eye over Time by Cohort
- Listing 3BB: Listing of Patients with Abnormal and/or Clinically Significant Labs
- Listing CC: Abnormal Physical Examination Listing by Patient
- Table 3DD: Mean Change in Continuous Laboratory Parameters by Cohort and Visit
- Listing 3EE: OCT Listing by Patient and Visit
- Figures 3FF-3HH: Central Retinal Thickness (OCT) for Study and Fellow Eyes in Cohort X
- Figures 3II-3KK: Macular Volume (OCT) for Study and Fellow Eyes in Cohort X
- Table 3LL: Change from Baseline in Vital Signs by Cohort and Visit
- Listing 4A: Static (GATE) Perimetry Data by Patient
- Figures 4B-4D: Volume of Full Field Hill of Vision Measured by Static (GATE) Perimetry by Patient in Cohort X
- Figures 4E-4G: 111pt grid-Volume of Full Field Hill of Vision Measured by Static (GATE) Perimetry by Patient in Cohort X
- Listing 4H: Kinetic (SKP) Perimetry Data by Patient
- Figures 4I-4K: SKP Data in Study Eyes by Patient in Cohort X
- Listing 4L: Full Field ERG Response (Study Eye) Amplitude and Implicit Time Data by Cohort, Patient and Visit
- Table 4M: Mean Peak Amplitudes and Latencies at Baseline (mfERG) by Cohort and Patient
- Table 4N: Central Field (Rings 1-3) Summary mfERG Data by Cohort and Patient
- Table 4O: Peripheral Field (Rings 4-6) Summary mfERG Data by Cohort and Patient
- Listing 5A: Detailed Listing of Immunologic Results from Blood Samples by Cohort and Patient
- Listing 5B: Biodistribution Endpoint Data

ADVERSE EVENT TABLE SHELL FOR TDU13600

PRIMARY SYSTEM ORGAN CLASS **HLGT: High Level Group Term** **HLT: High Level Term** **Preferred Term n(%)**	**Cohort 1 (1.4×10^5 TU) (N=3)**	**Cohort 2 (4.7×10^5 TU) (N=3)**	**Cohort 3 (1.4×10^6 TU) (N=3)**	**All Cohorts (N=9)**
Any Class	X (X%)	X (X%)	X (X%)	X (X%)
SOC1	X (X%)	X (X%)	X (X%)	X (X%)
HLGT1	X (X%)	X (X%)	X (X%)	X (X%)
HLT1	X (X%)	X (X%)	X (X%)	X (X%)
PT1	X (X%)	X (X%)	X (X%)	X (X%)
SOC2	X (X%)	X (X%)	X (X%)	X (X%)
HLGT1	X (X%)	X (X%)	X (X%)	X (X%)
HLT1	X (X%)	X (X%)	X (X%)	X (X%)
PT1	X (X%)	X (X%)	X (X%)	X (X%)
HLT2	X (X%)	X (X%)	X (X%)	X (X%)
PT2	X (X%)	X (X%)	X (X%)	X (X%)
HLGT2	X (X%)	X (X%)	X (X%)	X (X%)
HLT3	X (X%)	X (X%)	X (X%)	X (X%)
PT3	X (X%)	X (X%)	X (X%)	X (X%)

Generated on DDMMMYY HH:MM
By Path