STATISTICAL ANALYSIS PLAN

A Randomized, Double-masked, Vehicle-controlled Study Evaluating the Efficacy and Safety of Two Doses of OCS-01 compared to Vehicle in the Treatment of Inflammation and Pain Following Cataract Surgery

Sponsor: Oculis ehf.

Protocol Number: DX216

Author: Brian Kilgallen, M.S.
Senior Principal Biostatistician
Statistics & Data Corporation

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Statistical Analysis Plan Approval

Prepared by: _____ 18 Nov 2019

Brian Kilgallen, M.S. Date

Senior Principal Biostatistician

Statistics & Data Corporation

Reviewed by: _____ 18 Nov 2019

Rebecca Bates, M.S. Date

Director, Biostatistics

Statistics & Data Corporation

Approved by: _____ 11 Nov 2019

Fabio Baschiera Date

Vice President, Clinical Development

Oculis, ehf.

Approved by: _____ 15 Nov 2019

Sabri Markabi Date

Chief Scientific Officer

Oculis, ehf.

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List of Abbreviations

ADaM	Analysis Data Model
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BID	*Bis in die* (Twice Daily)
CI	Confidence Interval
CS	Clinically Significant
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
FAS	Full Analysis Set
HIPAA	Health Insurance Portability and Accountability Act of 1996
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing Not at Random
NCS	Not Clinically Significant
OD	*Oculus Dexter* (Right Eye)
OS	*Oculus Sinister* (Left Eye)
OU	*Oculus Uterque* (Both Eyes)
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
QD	*Quaque die* (Once Daily)
RTF	Rich Text Format
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics & Data Corporation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TLF	Tables, Listings, and Figures
WHO	World Health Organization

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol DX216, Amendment 1 dated 08-August-2019.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the clinical study report.

2. Study Objectives

The primary objective of this study is to evaluate the efficacy and safety of OCS-01 once daily (QD) and twice daily (BID) compared to placebo (vehicle) BID in the treatment of inflammation and pain following cataract surgery.

The secondary objective of this study is to evaluate the optimal dosing frequency of OCS-01 (QD versus BID) in the treatment of inflammation and pain following cataract surgery.

2.1 Study Variables

2.2 Primary Variables

The hierarchical primary efficacy measures are the absence of anterior chamber cells (i.e. score of '0') at Visit 6 (Day 15) and the absence of pain (i.e. score of '0') at Visit 4 (Day 4).

2.3 Secondary Variables

The secondary efficacy measures include:

- Absence of anterior chamber cells at Visits 4, 5, and 7 (Days 4, 8, and 22);
- Absence of pain at Visits 3, 5, 6, and 7 (Days 8, 15, and 22);
- Absence of flare at Visits 4, 5, 6, and 7 (Days 4, 8, 15, and 22).
- Absence of both anterior chamber cells and flare at Visits 4, 5, 6, and 7 (Days 4, 8, 15, and 22); and
- Use of rescue medication on or prior to each visit and overall.

2.4 Safety Variables

Safety variables to be summarized will include visual acuity, intraocular pressure (IOP), occurrence of adverse events (AE), and measurements from slit lamp biomicroscopy and dilated indirect ophthalmoscopy.

2.5 Statistical Hypotheses

The hierarchical statistical hypotheses for evaluating the objectives of the study are as follows:

Primary Endpoint:

H_{011}: The difference, between study eyes treated with OCS-01 BID and study eyes treated with placebo (vehicle), in the proportion of study eyes with absence of anterior chamber cells (score of '0') at Visit 6 (Day 15) = 0.

H_{111}: The difference, between study eyes treated with OCS-01 BID and study eyes treated with placebo (vehicle), in the proportion of study eyes with absence of anterior chamber cells (score of '0') at Visit 6 (Day 15) ≠ 0, with superiority claimed if the difference is greater than 0 (OCS-01 BID – placebo [vehicle]).

H_{012}: The difference, between study eyes treated with OCS-01 QD and study eyes treated with placebo (vehicle), in the proportion of study eyes with absence of anterior chamber cells (score of '0') at Visit 6 (Day 15) = 0.

H_{112}: The difference, between study eyes treated with OCS-01 QD and study eyes treated with placebo (vehicle), in the proportion of study eyes with absence of anterior chamber cells (score of '0') at Visit 6 (Day 15) ≠ 0, with superiority claimed if the difference is greater than 0 (OCS-01 QD – placebo [vehicle]).

Hierarchical Primary Endpoint:

H_{021}: The difference, between study eyes treated with OCS-01 BID and study eyes treated with placebo (vehicle), in the proportion of study eyes with absence of pain (score of '0') at Visit 4 (Day 4) = 0.

H_{121}: The difference, between study eyes treated with OCS-01 BID and study eyes treated with placebo (vehicle), in the proportion of study eyes with absence of pain (score of '0') at Visit 4 (Day 4) ≠ 0, with superiority claimed if the difference is greater than 0 (OCS-01 BID – placebo [vehicle]).

H_{022}: The difference, between study eyes treated with OCS-01 QD and study eyes treated with placebo (vehicle), in the proportion of study eyes with absence of pain (score of '0') at Visit 4 (Day 4) = 0.

H_{122}: The difference, between study eyes treated with OCS-01 QD and study eyes treated with placebo (vehicle), in the proportion of study eyes with absence of pain (score of '0') at Visit 4 (Day 4) ≠ 0, with superiority claimed if the difference is greater than 0 (OCS-01 QD – placebo [vehicle]).

Multiple comparison adjustments for testing OCS-01 BID and OCS-01 QD versus placebo (vehicle) in the absence of anterior chamber cells will not be made (i.e. the testing of H_{011} versus H_{111} and H_{012} versus H_{112} will both be completed at a 2-sided alpha = 0.10). A hierarchical testing strategy will be employed for testing absence of pain; statistical inference will only be made on the absence of pain endpoint if the corresponding OCS-01 dose (BID or QD) demonstrated statistical superiority over placebo (vehicle) in the absence of anterior chamber cells.

3. Study Design and Procedures

3.1 General Study Design

This study is a multi-center, randomized, double-masked, placebo (vehicle)-controlled study, designed to evaluate the efficacy and safety of OCS-01 ophthalmic suspension (QD versus BID) compared to placebo in treating inflammation and pain following cataract surgery.

Eligible subjects will be randomized 1:1:1 to receive OCS-01 QD, OCS-01 BID, or placebo BID. Subjects will dose 1 drop in the study eye BID for 14 days, beginning 1 day post-surgery in the operated eye. The study will last 20-52 days, including screening and a follow-up visit at Visit 7 (Day 22 ± 2).

3.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided in **Table 1**.

Table 1: Scheduled of Visits and Measurements

Study Parameter	Visit 1 (-28 to -1 Day(s) Prior to Surgery)	Visit 2 (Day 1, 18-30 h Post-Surgery)	Treatment Period				Follow-up
			Visit 3 (Day 2, telephone call)	Visit 4 (Day 4 ± 1)	Visit 5 (Day 8 ± 1)	Visit 6 (Day 15 ± 2)	Visit 7 (Day 22 ± 2)
Informed Consent / HIPAA	X						
Demographic Data	X						
Medical and Medication History	X						
Urine pregnancy Test	X						X
Review Inclusion / Exclusion Criteria	X	X					
Medical and Medications Update		X		X	X	X	X
Ocular Pain (Study Eye Only)	X	X	X	X	X	X	X
Pin-hole Visual Acuity	X	X		X	X	X	X
Slit lamp Biomicroscopy	X	X		X	X	X	X
Ocular Inflammation Assessment of the Anterior Chamber Cell and Flare (Study Eye Only)	X	X		X	X	X	X
Intraocular Pressure	X			X	X	X	X
Randomization		X					
Dilated Indirect Ophthalmoscopy	X						X
Dispense Study Medication and Dosing Diary		X					
AE Query		X		X	X	X	X
Exit from Study							X

4. Study Treatments

Subjects will be assigned to 1 of 3 possible study treatments in this study. The study treatments to be evaluated in this study are:

- OCS-01 ophthalmic suspension (QD) + Placebo (vehicle) (QD)
- OCS-01 ophthalmic suspension (BID)
- Placebo (vehicle) ophthalmic suspension (BID)

Each subject will receive a master kit containing an AM dosing box and a PM dosing box. Each dosing box will contain 2 aluminum pouches with 10 single-use vials each.

4.1 Method of Assigning Subjects to Treatment Groups

Each subject who signs an informed consent form (ICF) will be assigned a screening number. Screening numbers will be assigned in sequential order at each site beginning with 001 and will follow the two-digit site number (e.g. subject 077 at Site 99 will have Screening Number 99-077). Inclusion and exclusion criteria will be reviewed, and qualifying subjects will be enrolled into the study. The screening number will be used to identify subjects in all datasets and listings for this study.

At the Visit 2 / Day 1 visit, eligible subjects will be randomized in a 1:1:1 ratio, stratified by site, to receive either OCS-01 ophthalmic suspension (QD) + Placebo (vehicle) (QD), OCS-01 ophthalmic suspension (BID), or Placebo (vehicle) ophthalmic suspension (BID).

4.2 Masking and Unmasking

An independent biostatistician who is not otherwise involved in the study will generate the final, unmasked subject randomization as well as the final, unmasked kit list randomization. Interactive response technology will be used to provide randomization assignments.

As described in Section 4, each subject will receive a master kit containing an AM dosing box and a PM dosing box. For masking purposes, each dosing box and the pouches within it will be labeled either “AM” or “PM.” Dosing boxes and pouches will be labeled this way regardless of whether the product within the 2 boxes is the same (i.e. OCS-01 BID and placebo [vehicle] treatment arms) or different (i.e. OCS-01 QD).

5. Sample Size and Power Considerations

With a total of 150 subjects (50 subjects per treatment group: OCS-01 BID, OCS-01 QD, and placebo [vehicle] in the Full Analysis Set [FAS] [i.e. 1:1:1 randomization]), the study has 85% power to detect a statistically significant treatment difference between OCS-01 BID and placebo and between OCS-01 QD and placebo for the proportion of subjects with absence of cells on post-operative Visit 6 (Day 15), assuming a 2-sided alpha level of 0.10 and the proportion of subjects with absence of cells is 0.45 (active) and 0.20 (placebo [vehicle]).

Additionally, with this sample size, the study has 83% power to detect a statistically significant treatment difference between OCS-01 (BID or QD) and placebo for the proportion of subjects with absence of ocular pain on post-operative Visit 4 (Day 4), assuming a 2-sided alpha level of 0.10, and the proportion of subjects with absence of ocular pain is 0.50 (active) and 0.25 (placebo [vehicle]).

6. Data Preparation

6.1 Input Data

All reported study data will be recorded on the electronic case report forms (eCRF) supplied by Statistics & Data Corporation (SDC). Only the Principal Investigator and authorized study staff according to the Delegation of Responsibilities log are entitled to make entries in the eCRF.

After data are entered into the clinical study database, electronic edit checks and data review will be performed. All data validation specifications and procedures are detailed in the Data Validation Manual as a separate document. When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after data have been locked can only be made with the approval of the Sponsor and the clinical contract research organization (if applicable), in consultation with SDC.

All analyses outlined in this document will be carried out after the following have occurred:

- All data management requirements are met according to SDC standard operating procedures, including data entry, performance of edit and validation checks, documentation and resolution of data queries, and database lock with written authorization provided by appropriate SDC and Sponsor personnel.
- Protocol deviations have been identified and status defined (major/minor deviations).
- Analysis populations have been determined.
- Randomized treatment codes have been unmasked.

6.2 Output Data

Data from remote data capture and external data will be transferred to Biostatistics and incorporated into standard formats following the Study Data Tabulation Model (SDTM). Data will then be mapped to analysis datasets using the Analysis Data Model (ADaM). Both SDTM- and ADaM-formatted data will be used to create the subject listings, while all tables and figures will be based on the ADaM-formatted data.

SDTM will follow the SDTM version 1.4 model and will be implemented using the SDTM Implementation Guide version 3.2 and the SDTM Controlled Terminology version 2016-06-24. ADaM data will follow the ADaM version 2.1 model and will be implemented using the ADaM Implementation Guide version 1.3. Both

SDTM and ADaM will be validated using Pinnacle 21 version 2.2. Any discrepancies in the validation will be noted in reviewer's guides accompanying the final data transfers.

Define.xml will be created for SDTM and ADaM using the Define-XML version 2.0 model

7. Analysis Populations

7.1 Enrolled Subjects Population

The enrolled subjects population will consist of all subjects who have provided informed consent and have data in the clinical database.

7.2 Full Analysis Set

The full analysis set (FAS) will consist of all randomized subjects, analyzing subjects under the treatment to which they were randomized.

7.3 Per Protocol Population

The per protocol (PP) population is a subset of the FAS and includes subjects who remain in the study through Visit 6 (Day 15) (or who discontinue due to lack of efficacy or receive rescue medication prior to Visit 6 [Day 15]) with no major protocol violations that would affect the assessment of the primary efficacy endpoints of the study, analyzing subjects under the treatment received. Major protocol violations related to study inclusion or exclusion criteria, conduct of the trial, subject management, or subject assessment will be identified prior to unmasking treatment.

7.4 Safety Population

The Safety population includes all randomized subjects who receive at least 1 dose of study medication. The Safety population will be analyzed as treated and will be used for the safety analyses. No data will be excluded for any reason.

8. General Statistical Considerations

8.1 Unit of Analysis

For measurements taken at the subject level, the unit of analysis will be the individual subject and for measurements taken at the eye level, the unit of analysis will be the individual eye unless otherwise indicated. Where applicable, summaries by eye will present results separately for the study eye and for the non-study eye. Any outcomes (eg, adverse events) with reported location of OU will be counted as an event for both the study eye as well as the non-study eye.

Non-ocular AEs, medical history, and concomitant medication usage will be presented at the subject level, but ocular AEs, medical history, and concomitant medication usage will be presented at the eye level as appropriate.

8.2 Missing or Inconclusive Data Handling

8.2.1 Partial Dates

Imputation of partial or missing dates will be conducted in order to classify data as treatment-emergent or concomitant with treatment. Partial/missing start and end dates for AEs and concomitant medications will be imputed as follows:

Partial/missing start date:

- Dates with missing day only will be imputed as the 1st of the month unless the month and year are same as the month and year of first dose of study medication, in which case missing day will be imputed as the first dose day of study medication.
- Dates with both day and month missing will be imputed as 01-Jan unless the year is same as the year of first dose of study medication, in which case missing day and month will be imputed as the first dose day and month of study medication.
- Completely missing dates will be imputed as the first dose date of study medication unless the end date is on or before the first dose date of study medication, in which case missing date will be imputed as 1 Jan of the same year as the end date.

Partial/missing end date:

- Dates with missing day only will be imputed as the last day of the month unless the month and year are the same as the month and year of the last dose of study medication, in which case missing day will be imputed as the last dose day of study medication.
- Dates with both day and month missing will be imputed as 31 Dec unless the year is same as the year of the last dose of study medication, in which case missing day and month will be imputed as the last dose day and month of study medication.
- If the ongoing flag is missing or “Yes” then the date will not be imputed. If ongoing is “No” then the missing end date will be imputed as the last dose date.

The original dates will be displayed in data listings and the imputed dates will be used in derivations only (study day, treatment-emergence status, etc).

8.2.2 Missing Efficacy Data

The primary analyses of all efficacy data will use last observation carried forward (LOCF) to impute missing data; data for visits after a subject is discontinued for lack of efficacy or receives rescue medication will be imputed as failures for success/failure endpoints and will be imputed using LOCF for other endpoints. Additional sensitivity analyses based on alternate handling of missing values will be conducted, and described in further detail in Section 13.1.1.

8.2.3 Missing Safety Data

For all safety variables, missing data will not be imputed, observed values will be presented.

8.3 Definition of Baseline

Baseline is defined as the last non-missing measure prior to initiation of study treatment. Change from baseline will be calculated as follow-up visit value minus baseline value.

8.4 Data Analysis Conventions

All data analysis will be performed by SDC after the study is completed and the database has been locked. After the study database has been locked and any other prerequisites for unmasking are met (e.g. all protocol deviations have been classified as major or minor), unmasking will be done for the purpose of the primary analysis, and all planned tables, listings, and figures (TLF) will be generated.

Statistical programming and analyses will be performed using SAS® version 9.4 or higher. Output will be provided in rich text format (RTF) for tables and portable document format (PDF) for TLF using landscape orientation. All study data will be listed by subject, treatment, and visit (as applicable) based on all randomized subjects unless otherwise specified (e.g. demography data, which is also captured for screen failure subjects).

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values. Summaries for discrete variables will include counts and percentages. All percentages will be rounded to one decimal place (i.e. XX.X%). Differences between active treatment groups and placebo (vehicle) will be calculated as active minus placebo and change from baseline will be calculated as follow-up visit minus baseline.

Dates within subject data listings will be presented based on ISO 8601 standard, as DD-MMM-YYYY.

All efficacy analyses will use a 2-sided alpha = 0.10 test unless otherwise stated and corresponding 2-sided 90% and 95% confidence intervals (CI) will be presented as applicable. All p-values will be rounded to 4 decimal places; p-values less than 0.0001 will be presented as “<0.0001”; p-values greater than 0.9999 will be presented as “>0.9999.”

Unless otherwise specified, summaries will be presented by treatment group and (where applicable) eye and visit. Analysis by visit will be based on nominal visit identifier. Data from unscheduled visits, unscheduled time points, or unplanned repeat assessments will be included in the data listings. In general, these data will be excluded from the summary tables unless otherwise specified.

Efficacy summaries by treatment group will include the 3 protocol defined treatment groups. Summaries of subject disposition and baseline characteristics will include additional subject groupings defined as:

- OCS-01 Total, consisting of subjects in the OCS-01 QD + Placebo or OCS-01 BID treatment groups.
- All Subjects, consisting of all subjects in the analysis population, regardless of treatment group.

Summaries of safety variables will also include the OCS-01 Total treatment group (but not All Subjects group).

Subject data listings will be sorted by treatment group, subject number, visit/time point, and parameter as applicable. Subject data listings will use the largest applicable analysis population. In most cases this will be the Full Analysis Population (for assessments collected in randomized subjects) or the Safety Population (for assessments collected in randomized subjects where dosing is also relevant.

For multiple imputation analyses where a seed may be specified, the seed will be set to 8-digit numeric value corresponding to the database lock date in YYYYMMDD format (eg, 20190901). If multiple seeds are needed within a program, the seed will be based on a 9-digit numeric consisting of the database lock date in YYYYMMDD format concatenated by an additional integer denoting the invocation number (eg, the first invocation would be 201909011, second would be 201909012). In addition, twenty imputations will be used as starting quantity, if the fraction of missing information is >30% then this will be increased to 40 imputations (Graham 2007).

8.5 Adjustments for Multiplicity

The hierarchy of statistical hypotheses for testing is described in Section 2.5.

Multiple comparison adjustments for testing OCS-01 BID and OCS-01 QD versus placebo (vehicle) in the absence of anterior chamber cells will not be made (i.e. the testing of H_{011} versus H_{111} and H_{012} versus H_{112} will both be completed at a 2-sided alpha = 0.10). A hierarchical testing strategy will be employed for testing absence of pain; statistical inference will only be made on the absence of pain endpoint if the corresponding OCS-01 dose (BID or QD) demonstrated statistical superiority over placebo (vehicle) in the absence of anterior chamber cells.

Operationally, p-values from the predefined analyses within the SAP will be presented within all applicable tables, however if one or both doses are not significantly different from placebo for the anterior chamber cell variable, then p-values generated for comparisons of the ocular pain variable should be considered exploratory / nominal in nature.

9. Disposition of Subjects

Disposition of subjects will be summarized for the Enrolled Subjects population. Among enrolled subjects, the total number of subjects randomized and number of subjects not randomized (i.e. screen failure) will be summarized. The primary reason for screen failure (among screen failure subjects) will also be tabulated. A subject listing will be provided which includes randomization status and reason for screen failure for subjects not randomized.

Disposition of subjects will also be summarized among randomized subjects. The number of subjects in each of the analysis populations (FAS, PP, Safety population) as well as for each investigational site will be displayed by treatment group and overall. The number and percentage of subjects completing the study,

prematurely discontinuing from the study, and the reasons for study discontinuation will be summarized by treatment group and overall. A subject listing will be provided which includes the date and reason for premature study discontinuation.

The number and percentage of subjects with major protocol deviations will be summarized by eCRF deviation code (e.g., Inclusion/Exclusion deviation), treatment group, and overall for the FAS. Protocol deviations will be reviewed and classified as major or minor prior to database lock and unmasking. Major deviations will be defined as those deviations that potentially impact the primary outcome of the study. A subject listing will be provided which includes the date of the deviation, the deviation code, the deviation description, and the classification of whether the deviation was judged to be major or minor in a blinded review.

In addition, subject listings will be provided that include informed consent date, inclusion and exclusion criteria violations, and exclusions from the PP population.

Details of the study randomization, including randomization date and time, randomized treatment and actual treatment, will also be included within a subject listing.

10. Demographic and Pretreatment Variables

The demographic variables collected in this study include age, sex, childbearing potential, ethnicity, race, and iris color. Subjects who record more than one race will be grouped into a single category denoted as Multi-Racial. Iris color will be summarized at the subject level, with a category for heterochromia. Demographic variables will be summarized for the FAS and Safety population, separately.

Age (years) will be summarized, overall and by treatment, using continuous descriptive statistics. Age will also be categorized as follows: < 65 years and ≥ 65 years. Age will be reported in years and calculated using the following formula:

Age = (Informed Consent Date – Date of Birth) / 365.25, truncated as an integer

The number and percentage of subjects will be presented by treatment group and overall for age category, sex, childbearing potential status, race, ethnicity, and iris color.

A subject listing that includes all demographic variables will be provided.

11. Medical History and Concomitant Medications

11.1 Medical History

Medical history and ocular history will be summarized separately for the Full Analysis Set. Ocular medical history is a subset of the overall medical history and will include those medical history items where an eye location (right eye [OD], left eye [OS], or both eyes [OU]) has been specified.

Medical history and ocular history will be coded using Medical Dictionary for Regulatory Activities (MedDRA), version 22.0 (or higher).

Non-ocular medical history will be summarized using discrete summary statistics and presented by treatment group at the subject level by System Organ Class (SOC) and Preferred Term (PT). Ocular medical history will be summarized at the subject level by SOC and PT and separately for the study eye and non-study eye. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once.

Within table summaries, SOC will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all subjects within each SOC.

Listings of medical history will be generated separately for ocular and non-ocular data. The study eye will be identified within listings of ocular medical history.

Details of each subject's cataract surgery will also listed.

11.2 Prior and Concomitant Medications

Prior and concomitant medication usage will be summarized with the Safety population.

Prior and concomitant medications will be coded using World Health Organization (WHO) Drug Global (B3, March 2019 [or higher]) dictionary, and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] Level 4 classification) and preferred name. If the ATC Level 4 classification is not provided, the next lowest classification that is provided in the coding dictionary will be used. The preferred name will be defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients (e.g. multivitamins), then the drug name will be summarized as the preferred name. Any uncoded terms will be summarized under the ATC classification and preferred name of "Uncoded."

Prior medications are defined as those medications with an end date before first dose date of study administration. Concomitant medications are defined as those medications listed as having been taken (1) prior to initiation of study drug administration and continuing for any period of time following the first administration of study drug or (2) at any time following the first administration of study drug. With this definition, it should be noted it is possible for a medication to be both a prior and concomitant medication.

Ocular medications are a subset of the overall medications and consist of those medication records where the location field on the eCRF is marked as OD, OS, or OU. In addition, medications which are classified as 'non-ocular' on the eCRF but which have potential to impact anterior chamber cell count or ocular pain will be reclassified as an ocular medication for analysis. These medications will be identified via manual review of coded medication classes as well as review of the indication fields. For purposes of analysis, the eye location value for analysis will be defined as OU.

IOP lowering medications are a subset of medications where the investigator has indicated on the eCRF that the medication was used to lower IOP. Concomitant medications will be summarized separately for ocular and non-ocular medications. Concomitant ocular medications will be tabulated separately for study

eye and for non-study eye. Medications reported as OU will be summarized as a medication for both the study eye as well as the non-study eye.

Medications will be tabulated for each treatment group using frequencies and percentages. Subjects may have more than one medication per ATC text. At each level of subject summarization, a subject will be counted once if he/she reports one or more medications. Percentages will be based on the number of subjects in each treatment group.

The number and percent of subjects initiating IOP lowering medications will be summarized by treatment group at each post-BL visit as well as across all visits.

Listings of prior and concomitant medications will be generated separately for ocular and non-ocular data. A separate listing will be generated for IOP lowering medications.

Rescue medication usage is an efficacy measure for this study, analysis of rescue medication is described separately in Section 13.2.5.

12. Dosing Compliance and Treatment Exposure

12.1 Dosing Compliance

Details of individual administrations of study medication done at home by subjects are not captured within the clinical database, therefore dosing compliance will not be summarized.

12.2 Treatment Exposure

The number and percent of subjects receiving at least one dose of study medication (i.e. Safety population) will be summarized as part of subject disposition.

Although not captured directly on the CRF, additional variables related to study drug administration will also be derived for summarization:

- Study drug interruption (yes/no), where interruptions will be identified via presence of a TEAE where action taken with study drug was marked as ‘drug interrupted’ or a protocol deviation indicating study drug was interrupted
- Premature discontinuation of study drug (yes/no), where discontinuations will be idenfied via presence of a TEAE where action taken with study drug was marked as ‘drug withdrawn’ or a protocol deviation indicating study drug was prematurely discontinued. Subjects who discontinue the study prior to Visit 6 (Day 15) will also be reviewed to verify if study drug was prematurely discontinued or not.
- Study drug completion, defined as those subjects where premature discontinuation of study drug is not equal to ‘yes’

A blinded data review will be conducted prior to database lock and unblinding to identify any other cases of study drug interruption or premature discontinuation of study drug which are known to have occurred, but are not identified through the criteria above. The classifications from this final review will be used for analysis.

The number and percent of subjects with study drug interruption, premature discontinuation of study drug, and study drug completion will be summarized by treatment group.

Subject data listings will be generated to present details of study drug assignment, study drug replacement, as well as first instillation of study medication performed in-clinic on Day 1. Details from the study drug accountability assessment will also be listed.

13. Efficacy Analyses

13.1 Primary Analysis

The hierarchical primary efficacy measures are the absence of anterior chamber cells (i.e. score of '0') in the study eye at Visit 6 (Day 15) and the absence of pain (i.e. score of '0') at Visit 4 (Day 4).

The anterior chamber cell count will be recorded as the actual number of cells observed if ≤10 cells are seen, otherwise a range is reported. Anterior chamber cell count is assessed for study eye only. Refer to **Table 2** for details.

Table 2. Anterior Chamber Cell Counts and Grade

Anterior Chamber Cells	
Grade	**Cell Count**
0	0
1	1-10
2	11-25
3	26-50
4	>50

Ocular pain will be assessed by the patient at screening and at each follow-up visit, utilizing a numerical pain rating scale. Scores range from 0 to 10, where 0 = No Pain and 10 = Severe Pain, such that larger scores correspond to higher levels of pain.

The observed anterior chamber cell count at Visit 6 will be used and categorized for analysis as follows:

- Absence of anterior chamber cells: anterior chamber cells count of 0 / Grade 0
- Presence of anterior chamber cells: anterior chamber cells count of 1 or more / Grade 1, 2, 3, or 4

Within this analysis, missing values for visits after a subject is discontinued for lack of efficacy or values obtained after subject has received rescue medication will be imputed as failures (i.e. anterior chamber cells present) for analysis. For all other missing data, LOCF will be used to impute the missing anterior chamber cell count grade, and the LOCF value will then be categorized for analysis as "cells present" or "cells absent".

Derivation of the pain score and absence of pain (i.e. score of '0') variables at Visit 4 (Day 4) will follow the same approach for handling of missing data and handling of pain scores obtained following use of rescue medication.

The primary efficacy variables, the absence of anterior chamber cells at Visit 6 (Day 15) and the absence of pain at Visit 4 (Day 4), will be summarized by treatment group using discrete summary statistics, including 2-sided 90% CIs for the proportion in each treatment group based on Agresti-Coull method.

For each OCS-01 dose (QD and BID) separately, the primary efficacy analyses will first compare the proportion of study eyes with absence of anterior chamber cells (score of '0') between OCS-01 and placebo (vehicle) at Visit 6 (Day 15) using the Pearson chi-squared statistic (Fisher's exact test will be used if any expected cell count is less than 5).

SAS® code used to generate the chi-squared test, Fisher's exact test, and expected cell counts for comparison of OCS-01 BID with Placebo in anterior chamber cells response at Visit 6 is as follows:

```
proc freq;
  tables avalcat * trtp / chisq exact expected;
  where avisitn=6 and trtp in ('OCS-01 BID' 'Placebo (vehicle) BID');
run;
```

where

- trtp =Placebo (vehicle) BID; OCS-01 BID.
- avalcat = 'Absent'; 'Present'.

Comparison of OCS-01 QD versus placebo (vehicle) will be conducted in a similar manner, differing only by the treatment arms which are included within the comparison. Testing for each OCS-01 treatment group versus placebo (vehicle) for the absence of pain variable will use similar code.

If the proportion of study eyes with absence of anterior chamber cells (score of '0') is statistically significantly higher for OCS-01 versus placebo (vehicle) at a 2-sided alpha = 0.10 at Visit 6 (Day 15), for either dose of OCS-01 (BID or QD), then the study will be considered a success. The hierarchical hypothesis testing the proportion of study eyes with absence of pain (score of '0') at Visit 4 (Day 4) between the corresponding OCS-01 dose and placebo (vehicle) will be performed using the Pearson chi-squared statistic at a 2-sided alpha = 0.10 (Fisher's exact test will be used if any expected cell count is less than 5).

Anterior chamber cell grade in the study eye at Visit 6 (Day 15) will be summarized by treatment group with descriptive statistics for discrete outcome, including shift from baseline.

Ocular pain score at Visit 4 (Day 4) will be summarized by treatment group with descriptive statistics for continuous outcome, including change from baseline.

The primary efficacy analysis will be conducted using the FAS.

13.1.1 SENSITIVITY ANALYSES OF THE PRIMARY EFFICACY MEASURES

To check the robustness of primary efficacy analysis results, the previously described analyses of the primary efficacy measures will be repeated based on alternate handlings of missing data and major protocol deviations.

An analysis based on observed data only will be conducted using FAS population. Data from subject visits after discontinuation for lack of efficacy or receipt of rescue medication will set to failure (i.e. non-respnose) for this analysis, all other missing values will not be imputed. The denominator will be based on the number of subjects in the treatment group with a non-missing value for analysis, which may be lower than total number of subjects in the treatment group.

The analysis based on observed data using FAS described in previous paragraph will be repeated for PP population.

Additional sensitivity analysis will also be conducted based on multiple imputation using the FAS population. The multiple imputation procedure will be done on the anterior chamber cell count grade, rather than the dichotomoized status variable (absent or present), and after imputation the fully imputed anterior chamber cell count grades will be dichotomized for analysis. The imputation procedure will be applied as follows:

1. Values obtained after rescue medication usage (as well as those missing for other reasons such as study discontinuation, regardless of discontinuation reason), will initially be set to 'missing'.
2. For subjects with a non-monotone (intermittent) missing pattern, MCMC will be used to impute their missing intermittent anterior chamber cell count grades including treatment arm, baseline value, and anterior chamber cell count grade from previous visit(s) as explanatory variables in the model. This will be done 20 times limiting the imputation to in range results (i.e. imputed values will be constrained to be no less than 0.0, no more than 4.0, and will be rounded to nearest integer, consistent with values of Grade 0, 1, 2, 3, and 4 for anterior chamber cell grading).
3. The remaining missing data for all subjects with a monotone missing data pattern will be imputed using regression with treatment arm, baseline value, and anterior chamber cell count grade from previous visit(s) as explanatory variables in the model. This model will be run once for each of the imputed datasets limiting imputation to in range results.
4. In order to maintain consistency with other sensitivity analyses with respect to handling of values after rescue medication usage or values which were missing (prior to imputation) due to discontinuation for lack of efficacy, values for visits after a subject is discontinued for lack of efficacy or has received rescue medication which have an imputed value of 'Grade 0 (Cells Absent)' will be reclassified to 'Grade 1 (1-10 Cells)'.
5. The anterior chamber cell counts (grades) will be categorized in the fully imputed data to cells present or cells absent.
6. The estimated percentage of responders by treatment group will be presented based on the average proportion of responders in the multiply imputed datasets.
7. Chi-square statistics will be generated separately for each of the imputations. Following the approach described by Ratitch et al (Ratich 2013), a Wilson-Hilferty transformation (Wilson 1931) will be applied to the individual chi-square statistics to obtain the equivalent standard normal values and standard error (1.0), and the values from the 20 individual imputations will then be combined using standard approaches within SAS Proc MIANALYZE. The two-sided p-value obtained fom SAS Proc MIANALYZE will then be divided by 2 to obtain the final p-value.

SAS code for the multiple imputation is as follows:

```
proc mi out=outmi nimpute=20
  minimum=   0 0 0 0
```

```
  maximum=  4 4 4 4
  round =  1 1 1 1
  seed=<database lock date>1;
  mcmc impute=monotone;
  by trt01pn;
  var base v4val v5val v6val;
 run;

proc mi data=outmi out=outmi2 nimpute=1
  minimum= .   0 0 0 0
  maximum= .4 4 4 4
  round = . 1 1 1 1
  seed=<database lock date>2;
  class trt01pn;
  monotone Reg(v4val = trt01pn base);
  monotone Reg(v5val = trt01pn base v4val);
  monotone Reg(v6val = trt01pn base v4val v5val);
  var trt01pn base v4val v5val v6val;
  by _imputation_;
 run;
```

As an additional sensitivity analysis, a tipping point analysis based on binomial outcome will also be conducted. Mirroring the primary analysis, anterior chamber cell counts obtained after rescue medication or due to discontinuation for lack of efficacy will again be set to non-response (cells present), all other remaining missing values will be imputed as part of this procedure. The goal of the tipping point analysis is to identify what proportion of the unknown missing values would need to be responders to cause the conclusions change, i.e., under which there is no longer evidence of a treatment effect. Then, the plausibility of such assumptions would be discussed. With this approach, also described as a "tipping point analysis via exhaustive scenarios analysis" (O'Kelly, 2014), every possible combination of response (anterior chamber cells absent or present) is considered for all subjects with missing endpoint value, and the primary analysis is repeated for each of these scenarios. As an example, if we were to observe 3 missing endpoint values on the OCI-01 QD arm and 2 missing endpoint values on control arm, the primary analysis would be repeated assuming each of the following scenarios:

- Three subjects with anterior chamber cells absent in the OCI-01 QD arm and two subjects with anterior chamber cells absent in PBO arm
- Three subjects with anterior chamber cells absent in the OCI-01 QD arm and one subjects with anterior chamber cells absent in PBO arm and one subject with chamber cells present in PBO arm
- Three subjects with anterior chamber cells absent in the OCI-01 QD arm and zero subjects with anterior chamber cells absent in PBO arm and two subjects with chamber cells present in PBO arm
- Two subjects with anterior chamber cells absent and one subject with anterior chamber cells present in the OCI-01 QD arm, and two subjects with anterior chamber cells absent in PBO arm and so on, up to
- Zero subjects with anterior chamber cells absent and three subjects with anterior chamber cells present in the OCI-01 QD arm, and zero subjects with anterior chamber cells absent and two subject with anterior chamber cells present in the PBO arm

The primary analysis will be repeated based on all possible combinations with respect to the missing endpoint values, and the p-value generated for each scenario. A table will be produced to illustrate the p-values based on each combination of the potential outcomes among missing subjects for Placebo and

OCS treatment arms. Given that the nature of this analysis is to determine what conditions lead to reversal from a successful outcome to an unsuccessful outcome based on the unknown missing values, this summary will only be generated for the arm(s) that achieve statistical significance for the primary efficacy endpoint.

The approaches described above for analysis based on observed case as well as multiple imputation and tipping point approaches will also be applied to the absence of pain score measure at Visit 4 (Day 4). For multiple imputation approach, the corresponding SAS code will be revised to align to maximum value of 10.0 as well as the differing number of visits prior to endpoint.

13.1.2 Subgroup Analyses of the Primary Efficacy Analysis

Descriptive summary of the number and proportions of responders, along with 90% CI, for both primary efficacy measurments will be tabulated separately in subgroups of subjects based on usage (yes/no) of any systemic anti-inflammatory drugs prior to Day 15 (Visit 6).

A blinded review of all medications will be conducted prior to database lock and unblinding in order to properly classify each subject into the appropriate category.

13.2 Secondary Analyses

The FAS population will be used for the secondary analyses.

Unless otherwise noted, missing values for visits after a subject is discontinued for lack of efficacy or values obtained after subject has received rescue medication will be imputed as failures (e.g. anterior chamber cells present) for analysis. For all other missing data, LOCF will be used to impute the missing value. In the situation where anterior chamber cell count status is defined to be 'present' due to discontinuation for lack of efficacy or usage of rescue medication, but the LOCF value results in an imputed count of '0', then the anterior chamber cell count value will be imputed as grade 1 (1 – 10 cells) instead to maintain consistency across analyses as to whether or not anterior chamber cell counts were present or absent for the subject at a given time point. A similar approach will be made for imputation of the ocular pain score, where imputed value of '0' will be replaced by '1' if subject is otherwise classified as having pain present due to discontinuation for lack of efficacy or usage of rescue medication.

13.2.1 Anterior Chamber Cells

The anterior chamber cell grade at each visit and change from baseline / shift from baseline will be summarized by treatment group at Visits 4, 5, and 7 (Days 4, 8, and 22) using continuous and discrete summary statistics. The anterior chamber cell count grade over time will also be displayed graphically with the mean and 90% CI at BL and each post-BL visit.

The absence of presence of anterior chamber cells at each visit will be summarized with discrete summary statistics, along with 90% confidence interval for the proportion of subjects absent anterior chamber cells. For each OCS-01 dose (BID and QD) separately, the difference in the proportion of study eyes with absence of anterior chamber cells (score of '0') between OCS-01 and placebo (vehicle) at each post-Baseline visit

will be conducted using the Pearson chi-squared statistic (Fisher's exact test will be used if any expected cell count is less than 5).

The observed anterior chamber cell grade values will be listed by subject and visit.

13.2.2 Ocular Pain

Absence of ocular pain at each visit will be summarized by treatment group with discrete summary statistics, along with 90% confidence interval for the proportion of subjects absent ocular pain. For each OCS-01 dose (BID and QD) separately, the difference in the proportion of study eyes with absence of anterior chamber cells (score of '0') between OCS-01 and placebo (vehicle) at each post-Baseline visit will be conducted using the Pearson chi-squared statistic (Fisher's exact test will be used if any expected cell count is less than 5).

The ocular pain score, including change from Baseline, at each visit will be summarized by treatment group using continuous summary statistics.

The observed ocular pain scores will be listed by subject and visit.

13.2.3 Anterior Chamber Flare

Anterior chamber flare is graded on a 5-unit scale where 0 = None, 1 = Faint, 2 = Moderate (iris and lens details clear), 3 = Marked (iris and lens details hazy), and 4 = Intense (fibrin or plastic aqueous).

Anterior chamber flare grade, including absence of flare, will be be summarized by treatment group and analyzed at Visits 4, 5, 6, and 7 (Days 4, 8, 15, and 22) in the same fashion as described for the secondary analysis of anterior chamber cells.

The observed anterior chamber flare grade values will be listed by subject and visit.

13.2.4 Absence of Both Anterior Chamber Cells and Flare

A composite variable based on absence of both anterior chamber cells and flare (i.e., anterior chamber cell grade = 0 and anterior chamber flare grade = 0) will also be summarized.

Absence of both anterior chamber cells and flare at Visits 4, 5, 6, and 7 (Days 4, 8, 15, and 22) will be summarized by treatment group with discrete summary statistics along with 90% confidence interval for the proportion of subjects absent anterior chamber cells and flare. For each OCS-01 dose (BID and QD) separately, the difference in the proportion of study eyes with absence of anterior chamber cells (score of '0') between OCS-01 and placebo (vehicle) at each visit will be conducted using the Pearson chi-squared statistic (Fisher's exact test will be used if any expected cell count is less than 5).

13.2.5 Rescue Medication Usage

Rescue medications are defined for analysis as those concomitant medications where the eCRF question, "Was this concomitant medication utilized for Rescue" is answered "Yes," and location is the study eye.

Time to first rescue medication usage will be analyzed based on Kaplan-Meier approach by treatment group. Subjects will be considered to have an event at the date where rescue medication for study eye was

first initiated. Since rescue medication may be initiated at any time – at a scheduled visit or between scheduled visits – the timing of rescue medication usage will be based on the date in which rescue medication was started. Subjects who do not have any usage of rescue medication in the study eye will be censored at the date of the last visit. Subjects who discontinue prior to completing all treatment period visits will be evaluated based on the visits which are available.

Rescue medication will be listed by subject and medication.

14. Safety Analyses

All safety analyses will be conducted using the Safety population.

Analyses will be presented by treatment group. An additional "OCS-01 Total" group, consisting of all subjects in either OCS-01 treatment group, will also be included.

14.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug-related. Treatment-emergent adverse events (TEAE) are defined as any event that occurs or worsens on or after the day and time when first treatment is initiated.

All AEs will be coded for analysis using MedDRA, version 22.0 (or higher).

Ocular AEs are a subset of AEs and are identified as those AEs where the location field on the AE eCRF is marked as OD, OS, or OU.

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made irrespective of relationship to study drug or seriousness of the event and should be evaluated according to the following scale:

- *Mild:* AE is noticeable to the subject, but is easily tolerated and does not interfere with the subject's daily activities.
- *Moderate:* AE is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- *Severe*: AE is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

The relationship of each AE to the study drug should be determined by the Investigator using these explanations:

- *Supected*: A reasonable possibility exists that the study drug caused the AE.
- *Not Suspected*: A reasonable possibility does not exist that the study drug caused the AE.

The expectedness of an AE should be determined based upon existing safety information about the study drug using these explanations:

- *Unexpected:* an AE that is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed.
- *Expected:* an AE that is listed in the IB at the specificity and severity that has been observed.

An AE is classified as expected or not based on Investigator's assessment.

An overall summary will be presented that includes the number of TEAEs and the number and percentage of subjects who experienced at least one TEAE, by treatment group. This summary will include similar summaries of serious TEAEs, suspected treatment-related TEAEs, expected TEAEs, unexpected TEAEs, TEAEs leading to study drug discontinuation, TEAEs leading to death, and TEAEs by maximum severity. Results will be presented for all events (ocular and non-ocular) as well as separately for ocular and non-ocular events. Ocular events will be further separated into study eye versus non-study eye.

A summarization of non-ocular TEAEs will include the overall number of TEAEs and overall number and percentage of subjects who experienced at least one TEAE. The number of TEAEs and the number and percentage of subjects will also be tabulated by (primary) SOC and PT. Ocular TEAEs will be summarized in a similar manner, but with results further subdivided into study eye and non-study eye. Including the two above described analyses, summaries by SOC and PT will be provided for the following categories of AEs:

- Ocular TEAEs
- Non-ocular TEAEs
- Suspected treatment-related ocular TEAEs
- Suspected treatment-related non-ocular TEAEs
- Expected ocular TEAEs
- Expected non-ocular TEAEs
- Unexpected ocular TEAEs
- Unexpected non-ocular TEAEs
- Serious ocular TEAEs
- Serious non-ocular TEAEs

If a subject experiences the same PT multiple times within the same SOC, that subject will only be counted once for that PT witin that SOC. As with the PT, if a subject experiences multiple events within the same SOC, that subject will only be counted once for that SOC. In the summaries, SOC will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all subjects within each SOC.

Summaries of TEAEs by maximum severity will be presented for ocular AEs (separately for treated eye and non-study eye) and non-ocular AEs separately. The number of subjects with any TEAEs (along with percentages) will be tabulated by SOC and PT within each SOC by treatment group, along with maximum severity per subject for each PT. To count the number of subjects with any TEAEs, if a subject has multiple

TEAEs coded to the same PT within the same SOC, the subject will be counted once under the maximum severity.

Separate listings of AEs will be produced to list all AEs, AEs leading to study drug discontinuation, and serious AEs. TEAEs will be identified within the listings.

14.2 Pin-hole Visual Acuity

Pin-hole, logarithm of the minimum angle of resolution (logMAR) visual acuity is assessed at Visits 1, 2, 4, 5, 6, and 7 (Days -28 to -1, 1, 4, 8, 15, and 22) using an Early Treatment Diabetic Retinography Study (ETDRS) chart.

The observed and change from baseline in number of letters read correctly will be summarized for each eye (study eye, non-study eye) by visit and treatment group (including a group for all actively treated subjects) using continuous descriptive statistics.

The number and proportion of subjects with worsening in visual acuity from previous visit of ≥2 lines (equivalent to reduction in 0.2 logMAR or 10 letters) will be tabulated by visit.

A subject listing of visual acuity will also be produced. This listing will include a variable that indicates if an eye had a visual acuity worsening corresponding to ≥2 lines.

14.3 Slit-Lamp Biomicroscopy Examination

A slit-lamp biomicroscopy examination of the eyelid, conjunctiva, cornea, anterior chamber, iris, and lens will be performed at Visits 1, 2, 4, 5, 6, and 7 (Days -28 to -1, 1, 4, 8, 15, and 22). The results will be graded as normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS).

Shifts from baseline result to post-baseline result will be presented using counts and percentages in each shift category by visit and treatment group (including a group for all actively treated subjects). This summary will be produced by visit , separately for study eye and non-study eye.

A subject listing of the slit-lamp biomicroscopy parameters will also be produced.

14.4 Dilated Indirect Ophthalmoscopy

A dilated indirect ophthalmoscopy examination of the vitreous, retina, macula, choroid, and optic nerve will be performed at Visit 1 (Day -28 to -1) and Visit 7 (Day 22). The results will be graded as normal, abnormal NCS, or abnormal CS.

Shifts from baseline result to post-baseline result will be presented using counts and percentages in each shift category by treatment group and for all actively treated subjects. This summary will be produced by visit, separately for study eye and non-study eye.

A subject listing of the dilated indirect ophthalmoscopy results will also be produced.

14.5 Intraocular Pressure (IOP)

Subjects' IOP will be assessed in each eye at Visits 1, 4, 5, 6, and 7 (Days -28 to -1, 4, 8, 15, and 22) using a calibrated Goldmann application tonometer affixed to a slit lamp. The measurement procedure will be repeated on the same eye twice consecutively. If the measurements are within 2 mmHg or less of each other, the mean of the 2 readings will be calculated and recorded. If the 2 readings differ by more than 2 mmHg, a third (consecutive) reading will be taken and the median (middle) IOP will be recorded. All IOP measurements will be included within subject data listings, however the median value (i.e. the mean value when 2 measurements are made, or the median value when 3 measurements are available) will be used for descriptive summaries.

The (median) IOP values and changes from baseline for each eye (study eye and non-study eye) will be summarized using continuous descriptive statistics by visit and eye for each treatment group and for all actively treated subjects. The maximum post-BL IOP value per subject, which refers to largest post-BL value per subject and eye regardless of which post-BL visit, will be included within this summary. The number and proportion of study eyes with IOP elevations based on the following cutoffs will be summarized:

- An IOP value of 30 mmHg or more
- An increase from baseline in IOP of 10 mmHg or more

A subject listing of IOP will also be produced. Individual IOP values ≥ 30 mmHg or an increase from baseline value of ≥ 10 mmHg will be flagged within the listing.

The number and percent of subjects with post-BLIOP lowering procedures will be summarized by treatment group at each post-BL visit as well as across all visits.

A subject listing of any IOP lowering procedures will also be produced.

Analyses of concomitant IOP lowering medications is described previously, within Section 11.2.

14.6 Clinical Laboratory Data

Results from the urine pregnancy test at Visit 1 (Day -28 to -1) and Visit 7 (Day 22) will be listed by subject.

15. Interim Analyses

Interim analyses will not be performed.

16. Changes from Protocol-Stated Analyses

There are no changes from the protocol-stated analyses.

17. References

Allison, P. D. Missing Data. *Sage University Paper Series: Quantitative Applications in the Social Sciences; no. 07-136*: Sage Publications Ltd. 2001.

Graham JW, Olchowski AE, Gilreath TD. How Many Imputations are Really Needed? Some Practical Clarifications of Multiple Imputation Theory. *Prevention Science.* 2007 Sep 1;8(3):206-13.

O'Kelly M, Ratitch B. Clinical trials with missing data: A guide for practitioners. (1st Ed). 2014

Ratich, B., Lipkovich, I., Kelly, M., Combining Analysis Results from Mulitply Imputed Categorical Data. PharmaSUG 2013 – Paper SP03, 2013.

Wilson, E. B., Hilferty, M. M. The distribution of chi-square. *Proceedings of the National Academy of Sciences of the United States of America*, 17, 684-688. 1931.

18. Revision History

Documentation of revision to the SAP will commence after approval of the final version 1.0.

19. Tables

Tables that will be included in the topline delivery are shown in boldface font.

Table Number	Title	Population
Table 14.1.1.1	**Subject Disposition**	**Full Analysis Set**
Table 14.1.1.2	Reasons for Screen Failure	Enrolled Subjects Population
Table 14.1.2	**Demographics**	**Safety Population**
Table 14.1.3.1	Ocular Medical History	Full Analysis Set
Table 14.1.3.2	Non-Ocular Medical History	Full Analysis Set
Table 14.1.4.1	Ocular Concomitant Medications	Safety Population
Table 14.1.4.2	Non-Ocular Concomitant Medications	Safety Population
Table 14.1.4.3	Post-BL IOP Lowering Medications by Visit	Safety Population
Table 14.2.1.1	**Absence of Anterior Chamber Cells at Visit 6 (Day 15): Missing Values Imputed via LOCF**	**Full Analysis Set**
Table 14.2.1.2	Absence of Anterior Chamber Cells at Visit 6 (Day 15): Observed Case with Limited Imputation	Full Analysis Set
Table 14.2.1.3	Absence of Anterior Chamber Cells at Visit 6 (Day 15): Observed Case with Limited Imputation	Per Protocol Population
Table 14.2.1.4	Absence of Anterior Chamber Cells at Visit 6 (Day 15): Missing Values Imputed via MI	Full Analysis Set
Table 14.2.1.5	Absence of Anterior Chamber Cells at Day 15: Tipping Point Analysis	Full Analysis Set
Table 14.2.1.6	Absence of Anterior Chamber Cells at Visit 6 (Day 15) by Subgroup: Missing Values Imputed via LOCF	Full Analysis Set

Table 14.2.2.1	**Absence of Ocular Pain at Visit 4 (Day 4): Missing Values Imputed via LOCF**	**Full Analysis Set**
Table 14.2.2.2	Absence of Ocular Pain at Visit 4 (Day 4): Observed Case with Limited Imputation	Full Analysis Set
Table 14.2.2.3	Absence of Ocular Pain at Visit 4 (Day 4): Observed Case with Limited Imputation	Per Protocol Population
Table 14.2.2.4	Absence of Ocular Pain at Visit 4(Day 4): Missing Values Imputed via MI	Full Analysis Set
Table 14.2.2.5	Absence of Ocular Pain at Visit 4 (Day 4): Tipping Point Analysis	Full Analysis Set
Table 14.2.2.6	Absence of Ocular Pain at Visit 4 (Day 4) by Subgroup: Missing Values Imputed via LOCF	Full Analysis Set
Table 14.2.3	**Absence of Anterior Chamber Cells by Visit**	**Full Analysis Set**
Table 14.2.4.1	Anterior Chamber Cell Count by Visit: Categorical Summary	Full Analysis Set
Table 14.2.4.2	Anterior Chamber Cells Grade by Visit: Continuous Summary	Full Analysis Set
Table 14.2.5	**Absence of Ocular Pain by Visit**	**Full Analysis Set**
Table 14.2.6	Ocular Pain Score by Visit: Continuous Summary	Full Analysis Set
Table 14.2.7	Absence of Anterior Chamber Flare by Visit	Full Analysis Set
Table 14.2.8.1	Anterior Chamber Flare by Visit: Categorical Summary	Full Analysis Set
Table 14.2.8.2	Anterior Chamber Flare by Visit: Continuous Summary	Full Analysis Set
Table 14.2.9	Absence of Both Anterior Chamber Cells and Flare by Visit	Full Analysis Set
Table 14.2.10	**Rescue Medication Usage**	**Full Analysis Set**
Table 14.3.1.1	**Overall Summary of TEAEs**	**Safety Population**
Table 14.3.1.2.1	Ocular TEAEs by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.2.2	Non-Ocular TEAEs by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.3.1	Suspected Treatment-Related Ocular TEAEs by System Organ Class and Preferred Term	Safety Population

Table 14.3.1.3.2	Suspected Treatment-Related Non-Ocular TEAEs by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.4.1	Expected Ocular TEAEs by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.4.2	Expected Non-Ocular TEAEs by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.5.1	Unexpected Ocular TEAEs by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.5.2	Unexpected Non-Ocular TEAEs by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.6.1	Serious Ocular TEAEs by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.6.2	Serious Non-Ocular TEAEs by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.7.1	Ocular TEAEs by System Organ Class, Preferred Term, and Maximum Severity	Safety Population
Table 14.3.1.7.2	Non-Ocular TEAEs by System Organ Class, Preferred Term, and Maximum Severity	Safety Population
Table 14.3.2	Pin-Hole Visual Acuity	Safety Population
Table 14.3.3	Slit Lamp Biomicroscopy Shifts from Baseline to Post-Baseline	Safety Population
Table 14.3.4	Dilated Indirect Ophthalmoscopy Shifts from Baseline to Post-Baseline	Safety Population
Table 14.3.5.1	**Intraocular Pressure (mmHg)**	**Safety Population**
Table 14.3.5.2	Post-BL IOP Lowering Procedures by Visit	Safety Population
Table 14.3.6	Treatment Exposure	Safety Population

20. Listings

Listing Number	Title	Population
Listing 16.1.7	Randomization Schedule	Full Analysis Set
Listing 16.2.1	Subject Disposition	Full Analysis Set
Listing 16.2.2.1	Protocol Deviations	Full Analysis Set

Listing 16.2.2.1	Inclusion/Exclusion Criteria Violations	Full Analysis Set
Listing 16.2.3	Study Population Inclusion	Enrolled Subjects Population
Listing 16.2.4.1	Demographics	Enrolled Subjects Population
Listing 16.2.4.2.1	Ocular Medical History	Full Analysis Set
Listing 16.2.4.2.2	Non-Ocular Medical History	Full Analysis Set
Listing 16.2.4.3.1	Prior and Concomitant Ocular Medications	Safety Population
Listing 16.2.4.3.2	Prior and Concomitant IOP Lowering Medications	Safety Population
Listing 16.2.4.3.3	Prior and Concomitant Non-Ocular Medications	Safety Population
Listing 16.2.4.4	IOP Lowering Procedures	Safety Population
Listing 16.2.4.5	Cataract Surgery	Full Analysis Set
Listing 16.2.5.1	Study Drug Administration	Full Analysis Set
Listing 16.2.5.2	Study Drug Replacement	Safety Population
Listing 16.2.5.3	Study Drug Accountability	Full Analysis Set
Listing 16.2.6.1	Ocular Pain	Full Analysis Set
Listing 16.2.6.2	Anterior Chamber Cells and Flare	Full Analysis Set
Listing 16.2.7.1	Adverse Events	Full Analysis Set
Listing 16.2.7.2	Serious Adverse Events	Full Analysis Set
Listing 16.2.7.3	Adverse Events Leading to Study Drug Discontinuation	Safety Population
Listing 16.2.8.1	Urine Pregnancy Test	Full Analysis Set
Listing 16.2.9.1	Pin-Hole Visual Acuity	Full Analysis Set
Listing 16.2.9.2	Dilated Indirect Ophtalmoscopy	Full Analysis Set
Listing 16.2.9.3	Slit Lamp Biomicroscopy	Full Analysis Set
Listing 16.2.9.4	Intraocular Pressure	Full Analysis Set

21. Figures

Figure Number	Title	Population
Figure 14.2.1	Absence of Anterior Chamber Cells by Visit	Full Analysis Set
Figure 14.2.2	Mean Anterior Cell Count Grade by Visit	Full Analysis Set
Figure 14.2.3	Absence of Ocular Pain by Visit	Full Analysis Set