Statistical Analysis Plan
RTA 408-C-1307
Confidential

Title: A Multicenter, Randomized, Dose-Ranging, Double-Masked, Placebo-Controlled Phase 2 Study Evaluating the Safety and Efficacy of RTA 408 Ophthalmic Suspension for the Treatment of Ocular Inflammation and Pain following Ocular Surgery

Approval(s):

[redacted]

Sponsor	Protocol	Version	Date	Distribution
Reata	RTA 408-C-1307	1.0	13/FEB/2014	TMF [redacted] Reata

Table of Contents

List of Abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical Classification
BID	Bis in die (twice daily)
CRF	Case Report Form
CS	Clinically Significant
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
HIPAA	Health Information Portability and Accountability Act
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
LOGMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not clinically significant
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
RDC	Remote Data Capture
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics and Data Corporation, Incorporated
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
VA	Visual Acuity
WHO DDE	World Health Organization Drug Dictionary Enhanced

1. Introduction

The primary objective of this SAP is to describe the planned analyses and reporting for protocol RTA 408-C-1307.

The SAP describes the statistical methodologies that will be used to address the objectives of the above study and come to conclusions regarding the study objectives, ensuring their validity and suitability.

2. Study Objectives

The objective of this study is to evaluate the clinical efficacy and safety of RTA 408 Ophthalmic Suspension in two concentrations versus placebo in the treatment of patients with inflammation and pain following uncomplicated ocular surgery.

3. Study Variables

3.1 Primary Variables

The primary efficacy variables are the following:

1. Absence of anterior chamber cells (i.e., score of '0') at Visit 5 (Day 15) for:
    a. The 1.0% concentration of RTA 408 Ophthalmic Suspension compared to placebo; and
    b. The 0.5% concentration of RTA 408 Ophthalmic Suspension compared to placebo.
2. Absence of pain (i.e., score of '0') at Visit 3 (Day 4) for:
    a. The 1.0% concentration of RTA 408 Ophthalmic Suspension compared to placebo; to be tested if 1a is statistically significant in favor of the active arm; and
    b. The 0.5% concentration of RTA 408 Ophthalmic Suspension compared to placebo; to be tested if 1b is statistically significant in favor of the active arm.

3.2 Secondary Variables

The secondary efficacy variables include the following:

1. Absence of anterior chamber cells at Visits 3, 4, or 6 (Days 4, 8 or 21 respectively)
2. Absence of pain at Visits 4, 5 or 6 (Days 8, 15 or 21 respectively)
3. Absence of flare at Visits 3, 4, 5 or 6 (Days 4, 8, 15 or 21 respectively)

3.3 Safety Variables

The safety variables include the following:

- Slit Lamp Biomicroscopy
- Pin-hole Visual Acuity
- Intraocular Pressure
- Dilated Indirect Ophthalmoscopic Examination
- Adverse Events

4. Statistical Hypotheses

The null and alternative hypotheses are as follows:

H_{011}: The difference, between study eyes treated with the 1.0% concentration of RTA 408 Ophthalmic Suspension and study eyes treated with placebo, in the proportion of study eyes with absence of anterior chamber cells (score of 0) at Visit 5 (Day 15) = 0.

H_{A11}: The difference, between study eyes treated with the 1.0% concentration of RTA 408 Ophthalmic Suspension and study eyes treated with placebo in the proportion of study eyes with absence of anterior chamber cells (score of 0) at Visit 5 (Day 15) ≠ 0, with superiority claimed if the difference is greater than 0 (RTA 408 Ophthalmic Suspension – Placebo).

H_{012}: The difference, between study eyes treated with the 0.5% concentration of RTA 408 Ophthalmic Suspension and study eyes treated with Placebo, in the proportion of study eyes with absence of anterior chamber cells (score of 0) at Visit 5 (Day 15) = 0.

H_{A12}: The difference, between study eyes treated with the 0.5% concentration of RTA 408 Ophthalmic Suspension and study eyes treated with placebo in the proportion of study eyes with absence of anterior chamber cells (score of 0) at Visit 5 (Day 15) ≠ 0, with superiority claimed if the difference is greater than 0 (RTA 408 Ophthalmic Suspension – Placebo).

and

H_{021}: The difference, between study eyes treated with the 1.0% concentration of RTA 408 Ophthalmic Suspension and study eyes treated with placebo in the proportion of study eyes with absence of pain (score of 0) at Visit 3 (Day 4) = 0.

H_{A21}: The difference, between study eyes treated with the 1.0% concentration of RTA 408 Ophthalmic Suspension and study eyes treated with placebo in the proportion of study eyes with absence of pain (score of 0) at Visit 3 (Day 4) ≠ 0, with superiority claimed if the difference is greater than 0 (RTA 408 Ophthalmic Suspension – Placebo).

H_{022}: The difference, between study eyes treated with the 0.5% concentration of RTA 408 Ophthalmic Suspension and study eyes treated with placebo in the proportion of study eyes with absence of pain (score of 0) at Visit 3 (Day 4) = 0.

H_{A22}: The difference, between study eyes treated with the 0.5% concentration of RTA 408 Ophthalmic Suspension and study eyes treated with placebo in the proportion of study eyes with absence of pain (score of 0) at Visit 3 (Day 4) ≠ 0, with superiority claimed if the difference is greater than 0 (RTA 408 Ophthalmic Suspension – Placebo).

The primary analyses will first test the difference in the proportion of patients with absence of anterior chamber cells in the study eye between the 1.0% concentration of RTA 408 Ophthalmic Suspension and placebo and between the 0.5% concentration of RTA 408 Ophthalmic Suspension and placebo at Visit 5 (Day 15) using the Pearson chi-squared statistic at a 1-sided alpha=0.10.

If the proportion of patients with a grade of '0' for anterior chamber cells is statistically significantly higher for the 1.0% concentration versus placebo at a 1-sided alpha=0.10, then the hierarchical hypothesis testing will compare the proportion of patients with absence of ocular pain at Visit 3 (Day 4) between the 1.0% concentration of RTA 408 Ophthalmic Suspension and placebo using the Pearson chi-squared statistic at a 1-sided alpha=0.10.

If the proportion of patients with a grade of '0' for anterior chamber cells is statistically significantly higher for the 0.5% concentration versus placebo at a 1-sided alpha=0.10, then the hierarchical hypothesis will compare the proportion of patients with absence of ocular pain at Visit 3 (Day 4) between the 0.5% concentration of RTA 408 Ophthalmic Suspension and placebo using the Pearson chi-squared statistic at a one-sided alpha=0.10.

If the test of the difference in the proportion of study eyes with absence of anterior chamber cells is statistically significant in favor of the 1.0% or 0.5% concentration of RTA 408 Ophthalmic Suspension versus placebo, then the study will be considered a success and the concentration(s) of RTA 408 Ophthalmic Suspension showing statistical significance will be declared to be superior to placebo in the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15).

5. Sample Size and Power Considerations

[redacted]

6. General Statistical Considerations

All data analysis will be performed by [redacted]ter the study is completed and the database has been locked and released for un-masking. Statistical programming and analyses will be performed using SAS® Version 9.2 or higher. Output will be provided in RTF format for tables and PDF format for tables, listings, and figures. All study data will be listed by patient, treatment, and visit (as applicable).

Continuous and ordinal variables will be summarized using descriptive statistics (i.e., number of observations (n), arithmetic mean, standard deviation (SD), minimum, median, and maximum). Categorical variables will be summarized descriptively using counts and percentages. Means and medians will be rounded to one decimal more than the collected data; SDs will be rounded to two decimal place more than the collected data. All percentages will be rounded to one decimal place (i.e., XX.X%).

Unless otherwise specified, summaries will be presented by treatment group and visit. The baseline measure is defined as the last non-missing measure prior to initiation of investigational treatment, which is Visit 2 (Day 1) for all measures with the exception of the dilated indirect ophthalmoscopic examination where the Visit 1 (≥28 days prior to surgery) will serve as baseline. Differences between active treatment groups and placebo will be calculated as Active minus Placebo. Changes from baseline will be calculated as follow-up value minus baseline value. All statistical tests will be one-sided with a significance level of 0.10 ($\alpha = 0.10$). Confidence intervals (CI) for differences between treatment groups will be two-sided at 80% confidence as well as 95% confidence. All p values will be rounded to four 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".

All study data will be listed by patient, treatment, and visit (as applicable), based on all enrolled patients.

6.1 Unit of Analysis

The unit of analysis in this study will be the study eye for all efficacy and safety summaries. Additionally, non-ocular AEs will be presented at the patient level. Non-study eye safety summaries will also be presented as appropriate.

6.2 Adjustments for Multiplicity

To address the two primary efficacy variables employed in this study, the primary efficacy variables have been prioritized into a hierarchical structure. In order to test ocular pain for RTA Ophthalmic Suspension 1.0%, anterior chamber cells must have shown statistically significant improvements for RTA Ophthalmic Suspension 1.0% versus placebo using a one-sided significance level of 0.10. This same strategy is applicable to the 0.5% concentration of RTA Ophthalmic Suspension.

No multiplicity adjustments will be employed for the multiplicity of tests due to two concentrations of active.

6.3 Handling of Dropouts or Missing Data

The primary analyses of all efficacy data will use LOCF to impute missing data; data for visits after a patient is discontinued for lack of efficacy will be imputed as failures for success/failure endpoints and will be imputed using LOCF for other endpoints.

Per Protocol analyses will use observed data only, with the exception of patients who have missing data due to discontinuation of study treatment for lack of efficacy; for these patients, data after discontinuation will be imputed as failures.

To check robustness of results, sensitivity analyses of the primary efficacy data will be performed. These include analyses of observed data only, imputing data from patient visits after discontinuation for lack of efficacy as failures and analyses in which all missing data are imputed using multiple imputation methodology.

6.4 Unscheduled Visits

Unscheduled data, such as information from unscheduled visits or Investigator comments, will be included in the data listings. In general, these data will be excluded from the summary tables unless otherwise specified.

7. Study Design and Procedures

7.1 General Study Design

This Phase 2, multi-center, double-masked, randomized, placebo-controlled, dose-ranging, study is designed to evaluate the clinical efficacy and safety of RTA 408 Ophthalmic Suspension 0.5% and RTA 408 Ophthalmic Suspension 1.0% compared to placebo in patients following ocular surgery. Approximately 105 male and female patients at least 18 years of age undergoing unilateral cataract extraction via phacoemulsification in one eye and meeting all other study eligibility criteria will be randomized to receive treatment with one of the two study drugs or placebo. Scheduled visits are to occur as follows: Visit 1 (Screening, Day ≥-28), Visit 2 (Day 1; 24 ±6 hours post-surgery), Visit 3 (Day 4 ±1 day), Visit 4 (Day 8 ±1 day), Visit 5 (Day 15 +1 day) and Visit 6 (Day 21 ±1 day; Exit Visit).

7.2 Study Treatments

RTA 408 Ophthalmic Suspension 0.5% and 1.0% are the active study medications that will be investigated in this study. Placebo (Vehicle of RTA 408 Ophthalmic Suspension) is the control of choice for this study in order to demonstrate the true efficacy of the study drugs. Patients will instill one drop of study medication twice-daily (BID) in the eye that underwent surgery (study eye) in the morning and evening (approximately 12 hours apart) for 14 days.

7.3 Method of Assigning Patients to Treatment Groups

At Visit 1, patients who provide verbal and written informed consent will be assigned a unique 7-digit patient ID, which includes the 4-digit site number plus a unique 3-digit screening number (beginning with 001 within each site). Screening numbers must be assigned in ascending consecutive order. RTA 408 Ophthalmic Suspension 0.5%, RTA 408 Ophthalmic Suspension 1.0% or placebo will be randomly assigned to a sequential list of kit numbers at each site using a 1:1:1 assignment ratio. Sequentially numbered study drug kits will be provided to each investigational site, in accordance with

the site-specific randomized study drug kit list, which consists of sequential 5-digit medication ID numbers. The randomized study drug kit lists will be generated using a complete block design with a block size of 6. Patients who meet all eligibility criteria will be randomized on the first day post-surgery (Visit 2; Day 1) by assignment of the lowest 5-digit study drug kit number available at their investigative site. If a randomized patient is discontinued from the study for any reason, their randomized study drug kit number will not be reassigned. A back-up block of treatments will be available at each site to be used for study treatment replacement.

7.4 Masking and Unmasking

An independent biostatistician who is not otherwise involved in the trial will generate the complete randomized study drug kit list. The patient, Sponsor, Investigators and study staff will be masked during the randomization process and throughout the study.

With each shipment of study drug, sites will receive one emergency unmasking envelope for every study drug kit received, including the back-up study drug kits. The envelopes and kits will both be labeled with the same 5-digit study drug kit number. The envelopes are sealed and contain the unmasked treatment information for the corresponding study drug kit.

Envelopes should be stored in a secured location and should only be opened (i.e., breaking the randomization code for that patient) in the event of a medical emergency, or when knowing the treatment assignment is absolutely necessary for the medical management of the study patient. When possible (i.e., in non-emergent situations), the study sponsor or representative should be notified prior to unmasking study drug. In emergency situations, the investigator must notify the sponsor within 24 hours after determining that it is necessary to unmask the treatment assignment. If the investigator determines that emergency unmasking is necessary, the investigator should identify and retrieve the emergency unmasking envelope for the given patient. The emergency unmasking envelope should be opened by the designated site personnel. The investigator must also indicate in source documents and in the eCRF that the mask was broken and provide the date, time, and reason for breaking the mask. Patients should have their study drug discontinued immediately if treatment assignment is unmasked.

7.5 Schedule of Visits and Assessments

The schedule of visits and assessments is provided below.

Study Parameter	Visit 1 (≥ -28 Days Prior to Surgery)	Visit 2 (Day 1, 24 ± 6 hrs Post-Surgery)	Visit 3 (Day 4[2])	Visit 4 (Day 8[2])	Visit 5 (Day 15[3])	Visit 6 (Day 21[2], Exit or Early Exit Visit)
Informed Consent/HIPAA	X					
Demographic Data	X					
Medical and Medication	X					

Study Parameter	Visit 1 (≥ -28 Days Prior to Surgery)	Visit 2 (Day 1, 24 ± 6 hrs Post-Surgery)	Visit 3 (Day 4[2])	Visit 4 (Day 8[2])	Visit 5 (Day 15[3])	Visit 6 (Day 21[2], Exit or Early Exit Visit)
History						
Urine Pregnancy Test (for females of childbearing potential)	X					X
Review of Inclusion and Exclusion Criteria	X	X				
Medical and Medication History Update		X	X	X	X	X
Ocular Pain Assessment	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 Anterior Chamber Cell and Flare (at Slit-lamp Biomicroscopy)	X	X	X	X	X	X
Intraocular Pressure Assessment	X	X	X	X	X	X
Randomization of Study Patients		X				
Dilated Indirect Ophthalmoscopic Examination	X					X
Study Drug Instillation[1]		X				
Study Drug and Compliance Diary Instructions and Dispensation		X				
AE Query		X	X	X	X	X
Review of Study Drug Compliance Diary			X	X	X	X
Collection of Study Drug and Compliance Diary					X	X[4]
Exit from Study						X

[1] First study drug dose will be instilled in-office at Visit 2. Patients will instill study drug twice daily at-home in the morning and evening (approximately 12 hrs apart) between study visits, from Day 1 through Day 14.
[2] ±1 Day
[3] +1 Day
[4] In case of early termination or if patient did not return study drug at prior to Visit 5.

8. Data Preparation

All reported study data will be recorded on the eCRFs supplied by [redacted] using Oracle Remote Data Capture (RDC), version 4.5.3. Only the Principle 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 Reata Pharmaceuticals, Inc. and [redacted] in consultation with [redacted]

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

- All data management requirements are met according to [redacted] 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 [redacted] and Sponsor personnel;
- Protocol deviations have been identified and status defined (major/minor deviations);
- Analysis populations have been determined; and
- Randomized treatment codes have been unmasked.

9. Analysis Populations

9.1 Intent-to-Treat Population

The intent-to-treat (ITT) population consists of all patients who are randomized. All data will be included and no patients will be excluded because of protocol violations. The ITT population will be analyzed as randomized and will be used for the efficacy analyses.

9.2 Per Protocol

The Per Protocol (PP) population is a subset of the ITT population and includes patients who remain in the study through Visit 5 (Day 15) with no major protocol violations that would affect the assessment of the primary efficacy endpoints of the study [major protocol violations that would affect the assessment of the primary efficacy endpoints of the study will be determined and documented through a masked review of protocol violations prior to unmasking the study treatment assignments]. Patients without major protocol violations thought to affect the primary efficacy outcome who discontinue the study treatment due to lack of efficacy will be analyzed in the PP analysis with data after study treatment discontinuation imputed as failures for success/failure endpoints and will be imputed using last observation carried forward (LOCF) for the data obtained immediately prior to study medication discontinuation for other endpoints. Otherwise, this population will be analyzed as treated using observed data only for confirmatory analyses.

9.3 Safety

The Safety population includes all randomized patients who received at least one dose of investigational treatment. The Safety population will be analyzed as treated and will be used for the safety analyses. No data will be excluded for any reason.

10. Patient Disposition

Patient disposition will be presented in terms of the numbers and percentages of patients who were randomized. Patients who are not discontinued from the study will be considered study completers.

The total number of screened subjects with the number and percentage of screen failure subjects and reasons for screen failure will be displayed with the percentages calculated using total number of

screen failures as the denominator. The number of patients in each of the populations (ITT, PP and Safety) will be displayed by treatment and percentages will be calculated using randomized patients as the denominator.

The number and percentage of patients with major protocol deviations will be summarized by treatment group for all randomized patients. The protocol deviations that will be summarized include: non-compliance with any scheduled study visit, non-compliance with study treatment, use of disallowed concomitant medications, non-compliance with study inclusion or exclusion criteria, non-compliance with study assessment procedures and other. A patient listing will be provided that includes the date of the deviation, the deviation description and the classification of whether the deviation was judged to be major or minor.

The number and percentage of patients prematurely discontinued from study treatment and the reasons for study treatment discontinuation will be summarized by treatment group for all randomized patients. The reasons for study treatment discontinuation that will be summarized include: adverse event (AE), protocol violation, lack of efficacy, administrative reasons, sponsor termination of study, voluntary withdrawal, pregnancy and other. A patient listing will be provided that includes the date of and reason for premature study treatment discontinuation.

The number and percentage of patients prematurely discontinued from the study and the reasons for study discontinuation will be summarized by treatment group for all randomized patients. The reasons for study discontinuation that will be summarized include: adverse event (AE), protocol violation, lack of efficacy, administrative reasons, sponsor termination of study, voluntary withdrawal, pregnancy and other. A patient listing will be provided that includes the date of and reason for premature study discontinuation.

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

11. Demographic and Baseline Characteristics

The demographic variables collected in this study include age, gender, race, ethnicity and iris color. Patients who record more than one race will be grouped into a single category denoted as multi-racial. Demographic variables will be summarized for each of the analysis populations separately.

Age (years) will be summarized, overall and by treatment, using number of observations, mean, standard deviation, median, minimum and maximum values. 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) +1 / 365.25) truncated as an integer

The number and percentage of patients will be presented, overall and by treatment, for age category, gender, race, ethnicity and iris color (for the study eye only).
A patient listing that includes all demographic variables will be provided.

12. Medical History and Concomitant Medications

12.1 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 16.1.

Non-ocular medical history will be summarized using discrete summary statistics and presented overall and by treatment group at the patient and event level by System Organ Class (SOC) and Preferred Term (PT) using the ITT population. Ocular medical history will be similarly summarized at the patient level, separately for the study eye and fellow eye. If a patient 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 patient reports multiple conditions within the same SOC, that SOC will only be reported once. Listings of medical history will be generated.

12.2 Prior and Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary Enhanced (WHO DDE; Enhanced B2, September 2013) and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical (ATC) 4 classification) and generic term.

Prior medications are defined as those medications listed as having been taken with a stop date prior to study drug administration. Concomitant medications are defined as those medications listed as having been taken 1) prior to 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.

Prior and concomitant medications will be summarized using the ITT population. Medications will be tabulated for each treatment group using frequencies and percentages, with separate tables for non-ocular, study eye, and fellow eye medications. Patients may have more than 1 medication per ATC4 text. At each level of patient summarization, a patient will be counted once if he/she reports 1 or more medications. Percentages will be based on the number of patients in each treatment group. The listing for prior and concomitant medications will include the start and stop dates as well as the date of the first administration of study drug to facilitate identification of whether a medication was a prior or concomitant medication.

13. Dosing Compliance and Treatment Exposure

13.1 Dosing Compliance

Dosing compliance (% compliance) will be assessed by calculating the number of actual doses received and comparing that to the number of expected doses as follows:

$$\text{Compliance (\%)} = \frac{\text{Number of Actual Doses Received}}{\text{Number of Expected Doses}} \times 100\%$$

The number of actual doses received will be calculated from the number of expected doses - the number of missed doses recorded in the CRF and determined through review of the patient diary and the in-office instillations. The number of expected doses that will be used for calculating compliance will be calculated as 2x[(date of last dose – date of Visit 2 [Day 1]) +1] for all patients, regardless of study completion status.

A categorical dosing compliance variable will also be derived as compliant (≥75%) and non-compliant (<75%).

Dosing compliance (%) will be summarized using number of observations, mean, standard deviation, median, minimum and maximum for each treatment group. The compliance category defined above will be summarized with counts and percentages. A patient listing of dosing compliance will also be produced.

13.2 Treatment Exposure

Extent of treatment exposure will be calculated in days using the following:

Extent of Exposure (days) = (Date of last dose – date of Visit 2 [Day 1]) + 1

Extent of treatment exposure (days) for each patient exposed to study drug will be summarized using descriptive statistics for each treatment group. A patient listing of treatment exposure will also be produced.

14. Efficacy Analyses

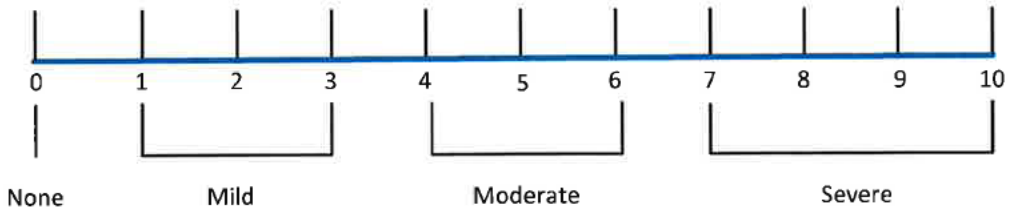
14.1 Primary Analysis

The anterior chamber cell grade for all study eyes will be recorded as well as the anterior chamber cell count if the actual number of cells observed is 10 cells or fewer (only white blood cells should be counted; red blood cells and pigment cells should not be counted). The 5-unit grading scale for anterior chamber cells is from 0 to 4 where 0 = 0 cells, 1 = 1 to 10 cells, 2 = 11 to 20 cells, 3 = 21 to 50 cells and 4 = >50 cells.

Ocular pain will be assessed by the patient utilizing a Numerical Pain Rating Scale (NPRS) graded from 0 to 10. Patients will assess the level of pain they are experiencing in the study eye at the time of the assessment.

The examiner will ask the patient the following question in reference to Figure 1 and will record the number selected by the subject on the appropriate eCRF.

On a scale of 0 to 10, in which 0 is no pain and 10 is the worst possible or unbearable pain, please mark on the scale the number that best describes the pain or discomfort you are feeling in the operated eye at this time. The middle of the scale (around 5) can be used to describe "moderate pain".*



The proportion of study eyes with absence of anterior chamber cells and the proportion of study eyes with absence of ocular pain will be presented overall and by treatment group using categorical summary statistics, including 90% confidence intervals.

Additionally, 80% and 95% confidence intervals will be constructed around the difference in proportions for each primary outcome using asymptotic normal approximations. Pearson's chi-square tests will be employed for statistical inference testing. Fisher's exact tests and exact confidence intervals will be employed in cases of expected counts less than five.

Additionally, a Cochran-Armitage test will be used to test for trend separately in the proportion of study eyes with absence of anterior chamber cells and the proportion of study eyes with absence of pain with increasing active concentration, using all three treatment groups.

The ITT population will be used for the primary analyses. In addition, confirmatory analyses will be performed on the PP population. The primary analysis variables will be presented in patient listings.

14.2 Secondary Analyses

All secondary analyses will be based on the ITT population. Raw scores will be presented in patient listings.

The secondary efficacy variables will be summarized at Days 4, 8, and 21 for absence of anterior chamber cells and at Days 8, 15 and 21 for absence of ocular pain using counts and percentages as described for the primary efficacy summaries. Additionally, anterior chamber cell grade and ocular pain score at each visit and change from baseline will be summarized using continuous and discrete summary statistics.

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). Absence of anterior chamber flare and anterior chamber flare grade and the sum of anterior chamber

cell and flare grade, including absence of both anterior chamber cell and flare, will be summarized at each visit in the same fashion as described for the primary analyses of anterior chamber cells and ocular pain.

The ITT population will be used for the secondary analyses. The secondary analysis variables will be presented in patient listings.

15. Safety

All safety analyses will be conducted using the Safety Population. All safety data will be listed by patient and visit, as applicable.

15.1 Adverse Events

An Adverse Event (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. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease occurring after the first dose of study drug, without any judgment about causality. Any pre-existing medical condition that worsens after first administration of the study drug will also be considered a new AE. The AE reporting period ends upon study exit. Study drug includes the investigational drug under evaluation and placebo given during any stage of the study. All AEs will be coded using the MedDRA dictionary, version 16.1.

Treatment-emergent adverse events (TEAEs) are defined as any event that occurs or worsens on or after the day that randomized study treatment is initiated. Adverse events recorded in the eCRF which began prior to treatment will not be included in the summary tables but will be included in the AE data listings.

An overall summary will be presented that includes the number of TEAEs and the number and percentage of patients who experienced at least one TEAE, by treatment group and overall. This summary will also include breakdowns of TEAEs further categorized as ocular (study eye and fellow eye separately) or non-ocular, serious TEAEs (SAEs), TEAEs by maximum severity, TEAEs by maximum relationship, and AEs leading to patient withdrawal.

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 patient. 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:* Event is noticeable to the patient, but is easily tolerated and does not interfere with the patient's daily activities.
- *Moderate:* Event is bothersome, possibly requiring additional therapy, and may interfere with the patient's daily activities.

- *Severe*: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the patient's daily activities.

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

- *Suspected*: 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.

Additional summaries of TEAEs will be provided showing the number and percentage of patients who experienced at least one TEAE. These summaries will be presented by system organ class (SOC) and preferred term (PT). Non-ocular TEAEs will be summarized using discrete summary statistics and presented by treatment group at the patient and event level by System Organ Class (SOC) and Preferred Term (PT). Ocular TEAEs will be similarly summarized at the patient level for study and fellow eyes separately. If a patient 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 patient reports multiple conditions within the same SOC, that SOC will only be reported once. The occurrence of non-ocular and ocular TEAEs will also be tabulated by SOC and PT for the following: maximal severity and suspected relationship to study drug.

Separate listings will be provided for all AEs, AEs leading to treatment discontinuation, and SAEs.

15.2 Slit-Lamp Biomicroscopy

A slit-lamp biomicroscopy examination of the cornea, conjunctiva, anterior chamber, iris, lens, and lid will be performed for both eyes at each visit. The results will be graded as normal, abnormal not clinically significant (NCS) or abnormal clinically significant (CS).

The results will be summarized using counts and percentages for each treatment group and for all patients combined at each visit for each eye (study eye and non-study eye). Percentages will be based on the number of patients in each treatment group with responses. Shift tables for the slit-lamp biomicroscopy parameters will also be provided comparing each follow-up visit to baseline (Visit 2 [Day 1]). A patient listing of the slit-lamp biomicroscopy parameters will also be produced.

15.3 Dilated Indirect Ophthalmoscopic Examination

A dilated indirect ophthalmoscopic examination of the vitreous, retina, macula, choroid and optic nerve will be performed at Visit 1 (≥28 days prior to surgery) and Visit 6 (Day 21). The results will be graded as normal, abnormal NCS or abnormal CS.

The results will be summarized using counts and percentages for each treatment group and for all patients combined at each visit for each eye (study eye and non-study eye). Percentages will be based on the number of patients in each treatment group with responses. Shift tables for the dilated

indirect ophthalmoscopic examination parameters will also be provided comparing Visit 6 (Day 21) to baseline (Visit 1; ≥28 days prior to surgery). A patient listing of the dilated indirect ophthalmoscopic examination parameters will also be produced.

15.4 Pin-Hole Visual Acuity (ETDRS)

The logarithm of the minimum angle of resolution (logMAR) pin-hole visual acuity is assessed at each visit using an EDTRS chart. Pin-hole visual acuity should be done with a pin-hole occluder.

The observed and change from baseline pin-hole visual acuity will be summarized for each eye (study eye and non-study eye) using descriptive statistics (number of observations, mean, standard deviation (SD), median, minimum, and maximum values) by visit for each treatment group and for all patients combined. In addition, the proportion of patients with a worsening (increase) in their logMAR pin-hole visual acuity from the previous visit of ≥2 lines will be presented using frequency counts and percentages. A patient listing of pin-hole visual acuity will also be produced.

15.5 Intraocular Pressure (IOP)

Intraocular pressure (IOP) will be assessed in both eyes by Goldman applanation tonometry at each visit. Results will be taken from a single measurement and will be recorded in mmHg.

The IOP values and changes from baseline for each eye (study eye and non-study eye) will be summarized using descriptive statistics (number of observations, mean, SD, median, minimum, and maximum values) by visit and eye for each treatment group and for all patients combined. In addition, the proportion of patients with an increase in IOP ≥10 mm Hg from baseline and the proportion of patients with an IOP ≥30 mm Hg at the visit will be presented using frequency counts and percentages. A patient listing of IOP will also be produced.

16. Interim Analyses

There are no planned interim analyses.

17. Changes from Protocol-Stated Analyses

The imputation methodology for the Per Protocol population, described in Section 9.2 of this SAP, differs from that described in the Protocol. The SAP accurately reflects how data will be handled for patients who are discontinued from study treatment due to lack of efficacy.

18. Reporting Conventions

Reporting conventions will adhere when possible to the International Conference on Harmonization (ICH) Guidance E3, "Structure and Content of Clinical Study Reports". All tables and listings will be presented in landscape format. All SAS output for tables and listings will be distributed in PDF files.

19. Revisions History

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

20. Tables

Table Number	Title	Population
14.1.1	Summary of Analysis Populations, All Patients	Intent-to-Treat
14.2.2.1	Patient Disposition	Intent-to-Treat
14.1.2.2	Patient Disposition	Per Protocol
14.1.3	Significant Protocol Deviations	Safety
14.1.4.1	Demographic Characteristics	Safety
14.1.4.2	Demographic Characteristics	Intent-to-Treat
14.1.4.3	Demographic Characteristics	Per Protocol
14.1.5.1	Non-Ocular Medical History	Intent-to-Treat
14.1.5.2	Ocular Medical History	Intent-to-Treat
14.1.6.1	Non-Ocular Prior and Concomitant Medication Use, Classified by WHO ATC Drug Classification	Intent-to-Treat
14.1.6.2	Ocular Prior and Concomitant Medication Use, Classified by WHO ATC Drug Classification	Intent-to-Treat
14.2.1.1	Absence of Anterior Chamber Cells at Day 15 and Ocular Pain at Day 4, Last Observation Carried Forward	Intent-to-Treat
14.2.1.2	Absence of Anterior Chamber Cells at Day 15 and Ocular Pain at Day 4, Observed Data	Intent-to-Treat
14.2.1.3	Absence of Anterior Chamber Cells at Day 15 and Ocular Pain at Day 4, Missing Data Imputed as Failures	Intent-to-Treat
14.2.1.4	Absence of Anterior Chamber Cells at Day 15 and Ocular Pain at Day 4, Observed Data	Per Protocol
14.2.2.1	Absence of Anterior Chamber Cells by Visit	Intent-to-Treat
14.2.2.2	Absence of Anterior Chamber Flare by Visit	Intent-to-Treat
14.2.2.3	Absence of Anterior Chamber Cells and Flare by Visit	Intent-to-Treat
14.2.2.4	Absence of Ocular Pain by Visit	Intent-to-Treat
14.2.3.1	Anterior Chamber Cells Grade by Visit	Intent-to-Treat
14.2.3.2	Anterior Chamber Flare Grade by Visit	Intent-to-Treat
14.2.3.3	Sum of Anterior Chamber Cells and Flare Grades by Visit	Intent-to-Treat
14.2.3.4	Ocular Pain Score by Visit	Intent-to-Treat
14.3.1.1	Summary of Treatment Emergent Adverse Events	Safety
14.3.1.2	Treatment-Emergent Adverse Events by System Organ Class	Safety
14.3.1.3	Treatment-Emergent Adverse Events by System Organ Class and Severity	Safety
14.3.1.4	Treatment-Emergent Adverse Events by System Organ Class and Relationship to Study Drug	Safety
14.3.1.5	Serious Treatment-Emergent Adverse Events by System Organ Class	Safety
14.3.1.6	Treatment-Emergent Adverse Events Leading to Patient Discontinuation by System Organ Class	Safety
14.3.2.1.1	Slit Lamp Biomicroscopy Findings	Safety
14.3.2.1.2	Slit Lamp Biomicroscopy Findings – Shift Table	Safety
14.3.2.2.1	Dilated Indirect Ophthalmoscopic Examination Findings	Safety
14.3.2.2.2	Dilated Indirect Ophthalmoscopic Examination Findings – Shift Table	Safety
14.3.2.3	Pin-Hole Visual Acuity	Safety

Table Number	Title	Population
14.3.2.4	Intraocular Pressure (IOP)	Safety
14.3.3	Treatment Exposure	Safety
14.3.4	Dosing Compliance	Safety

21. Listings

Listing Number	Title	Population
16.1.7	Randomization Schedule	Intent-to-Treat
16.2.1.1	Patient Disposition and Informed Consent	Intent-to-Treat
16.2.1.2	Inclusion/Exclusion Criteria	Intent-to-Treat
16.2.2	Protocol Deviations	Intent-to-Treat
16.2.3	Patients Excluded from Study Populations	Intent-to-Treat
16.2.4.1	Demographics	Intent-to-Treat
16.2.4.2	Medical History	Intent-to-Treat
16.2.4.3	Prior and Concomitant Medications	Safety
16.2.5	Study Drug Dosing Compliance and Exposure	Intent-to-Treat
16.2.6.1	Ocular Inflammation Assessment of Anterior Chamber Cell and Flare	Intent-to-Treat
16.2.6.2	Ocular Pain Assessment	Intent-to-Treat
16.2.7.1	All Adverse Events	Safety
16.2.7.2	Adverse Events Leading to Treatment Discontinuation	Safety
16.2.7.3	Serious Adverse Events	Safety
16.2.8	Pregnancy Test Results	Safety
16.3.2.1	Intraocular Pressure (IOP)	Safety
16.3.2.2	Slit Lamp Biomicroscopy	Safety
16.3.2.3	Pin-Hole Visual Acuity (ETDRS)	Safety
16.3.2.4	Dilated Indirect Ophthalmoscopic Examination	Safety

22. Figures

Figure Number	Title	Population
14.2.1.1	Absence of Anterior Chamber Cells at Each Visit	Intent-to-Treat
14.2.1.2	Absence of Ocular Pain at Each Visit	Intent-to-Treat
14.2.2.1	Anterior Chamber Cells at Each Visit	Intent-to-Treat
14.2.2.2	Ocular Pain at Each Visit	Intent-to-Treat