BAUSCH + LOMB

STATISTICAL ANALYSIS PLAN

Protocol Title:	A Randomized, Multicenter, Double Masked, Parallel-Group Study Assessing the Safety and Efficacy of Loteprednol Etabonate Ophthalmic Gel, 0.5% versus Prednisolone Acetate Ophthalmic Suspension, 1% for the Treatment of Intraocular Inflammation Following Surgery for Childhood Cataract
Protocol number:	670
Phase:	IV
Protocol Version:	Amendment 6
Protocol Date:	22 May 2013
Author:	Xiao Wang, MS
Version:	2.0
Date:	12 April 2017

SIGNATURES:

Analysis Plan Approval

Prepared by:

Xiao Wang, MS
Associate Biostatistician
Statistics & Data Corporation

Date

Reviewed by:

Kirk Bateman, MS
Director of Biostatistics
Statistics & Data Corporation

Date

Approved by:

Gary Mosehauer, MS
Principal Statistician
Bausch & Lomb, Inc.

Date

TABLE OF CONTENTS

List of Abbreviations

Abbreviation/ Acronym	Term
ACI	Anterior Chamber Inflammation
AE	Adverse Event
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
AP	Asia Pacific
BAK	Benzalkonium Chloride
BID	Twice per day
CI	Confidence Interval
eCRF	Electronic Case Report Form
EU	European Union
IOL	Intraocular Lens
IOP	Intraocular Pressure
ITT	Intent to Treat Population
LE	Loteprednol Etabonate
LOCF	Last Observation Carried Forward
LSmean	Least Square Mean
MedDRA	Medical Dictionary for Regulatory Affairs
OTC	Over the Counter
PP	Per Protocol Population
QD	Once per day
QID	Four times per day
SAF	Safety Population
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
TEAE	Treatment Emergent Adverse Event
SD	Standard Deviation
US	United States
VA	Visual Acuity
WHO	World Health Organization

1 Administrative Structure

This study is being conducted under the sponsorship of Bausch + Lomb, Inc.

2 Data Quality Assurance

The study monitors will be responsible for reviewing, verifying, and querying discrepant findings in the data recorded on the electronic case report forms (eCRFs) and the Investigators will be responsible for accuracy of the recorded data and answering all discrepant queries. The eCRFs will be submitted electronically via an electronic data capture system for quality assurance review, data entry, and statistical analysis.

3 Introduction

This document describes the statistical analyses and data presentations to be performed on this Phase IV, randomized, parallel group, double-masked, multi-center study of the safety and efficacy of Loteprednol Etabonate Ophthalmic Gel, 0.5% (QID) versus Prednisolone Acetate Ophthalmic Suspension, 1% (QID) for the treatment of intraocular inflammation following surgery for childhood cataract.

The purpose of this statistical analysis plan (SAP) is to ensure the credibility of the study findings by specifying the statistical approaches to the analysis of the data prior to database lock. This SAP covers the planned analyses of all data collected on the eCRFs, and will identify handling of data issues. The statistical analysis plan presented in this document will supersede the statistical analysis methods described in the clinical protocol. Any deviations/changes from the planned analyses described in this SAP will be identified, with justification, in the appropriate section of the clinical study report. This SAP is based on the final Protocol Study #670, amendment 6, dated 22 May, 2013 and on Administrative Change Memo 1, dated 19 Aug 2013.

4 Study Objective

The primary study objective is to compare the efficacy and safety of Loteprednol Etabonate (LE) Ophthalmic Gel, 0.5% to Prednisolone Acetate Ophthalmic Suspension, 1% for the treatment of postoperative inflammation following ocular surgery for childhood cataract.

5 Study Methods

5.1 Study Design

This study is a randomized, double-masked, parallel-group, active-controlled, multicenter study involving approximately 10 investigative sites in the United States (US), European Union (EU), and Asia Pacific (AP).

A total of 140 subjects aged 0-11 years will be randomized in a 1:1 ratio to LE Ophthalmic Gel, 0.5% or Prednisolone Acetate Ophthalmic Suspension, 1%. Of the 140 randomized subjects, at least 60 subjects (approximately 30 subjects per treatment group) will be in the age range from 0-3 years. Prednisolone Acetate Ophthalmic Suspension, 1% was chosen as the active-control because it has a long history as the standard of care for pediatric cataract surgeries in the US.

Study duration will be approximately 11-19 weeks from screening to the last visit (Visit 8, Postoperative Day 90). Subjects will visit the clinic eight times. Visit 1 will be the Screening Visit and will occur up to a maximum of 29 days prior to surgery. Visit 2 will be on the day of surgery. At the end of surgery on Visit 2, eligibility for randomization into the study will be assessed and, if appropriate, subjects will be randomized at this time. Randomized subjects will complete postoperative study Visits 3 through 8 (Postoperative Days 1, 7, 14, 28, 42, and 90, respectively).

Subject's eyes meeting eligibility criteria at both Visit 1 (Screening) and Visit 2 (Surgery/Randomization) were randomized to receive study medication. If both eyes of a subject underwent routine, uncomplicated surgery at Visit 2 (Surgery/Randomization) and met eligibility criteria, the subject's right eye was considered the study eye. In the event that the subject required surgery on the contralateral eye at any time during the study, the fellow eye was treated with standard of care medication.

The subject will receive the first dose of study drug by the unmasked designee at the end of the surgery. Either the unmasked designee or the subject's parent/legal guardian will then administer 1 to 2 drops of study drug to the lower cul-de-sac of the study eye once in the evening on the day of surgery and then 4 times a day (QID), at approximately 4 hour intervals, beginning on the morning after surgery. QID dosing will continue until postoperative day 14, including dosing at appropriate time intervals on the day of a visit. Treatment will be tapered by altering the frequency of study drug dosing to twice a day (BID) during the intervalbetween postoperative days 15 and 21. Treatment will be further tapered to once a day (QD) from postoperative day 22 until day 28, with the last dose being administered on the day prior to Visit 6 (Postoperative Day). No study drug doses were delivered after Visit 6, and subjects returned for post-dosing assessments at Visit 7 (Day 42) and Visit 8 (Day 90). Subjects then exited from the study.28).

Schedule of Visits and Parameters

All study tasks should be performed by qualified study site personnel as indicated on the delegation of authority log under the supervision of the Principal Investigator. Furthermore, all ocular signs must be evaluated by an ophthalmologist.

PROCEDURE/ASSESSMENTS[1]	**Visit 1** Screening	**Visit 2** Surgery/Randomization /Begin Treatment	**Visit 3** Follow-up	**Visit 4** Follow-up	**Visit 5** Follow-up	**Visit 6** Follow-up/End Treatment	**Visit 7** Follow-up	**Visit 8** Study Exit
	Day -15 (±14 days)	Day 0[2]	Day 1[3]	Day 7 (±2 days)	Day 14 (±3 days)	Day 28 (±7 days)	Day 42 (±7 days)	Day 90 (±14 days)
Informed consent, assent (when applicable), and authorization as appropriate for local privacy regulations	X							
Demographic data	X							
Current and relevant medical and ocular history	X							
Ocular symptoms	X		X	X	X	X	X	X
VA assessment	X	X	X	X	X	X	X	X
Slit lamp (biomicroscopy or magnifying lens with penlight)[4]	X	X	X	X	X	X	X	X
IOP (Goldmann or equivalent)[4]	X	X	X	X	X	X	X	X
Fundoscopy[5]		X	X		X			X
Eligibility determination	X	X						
Randomization		X						
AEs[6]/Concomitant medications	X	X	X	X	X	X	X	X
Weigh study drug and inspect diaries		X	X	X	X	X		
Dispense study drug and diaries		X[7]	X	X	X			
Collect study drug and diaries						X		
Exit subject								X

[1] All ophthalmic assessments will be performed bilaterally.
[2] Visit 2 must occur within 29 days of Visit 1. Screening and surgery cannot take place on the same day.
[3] Visit 3 (postoperative day 1) should occur on the next calendar day post-surgery.
[4] Every effort should be made to obtain slit lamp assessments and the assessment with the 20 dpt magnifying lens and penlight should only be performed if a slit lamp or handheld slit lamp examination cannot be performed. Once one of the methods has been chosen it should be employed throughout the study for each subject. IOP should also be measured with the same method throughout the study for each subject.
[5] Fundoscopy will be performed bilaterally either at Visit 2 (surgery/randomization) or Visit 3 (postoperative day 1), at Visit 5 (postoperative day 14 ±3 days), and at Visit 8 (postoperative day 90 ±14 days).
[6] Collection of AEs extends from the time the subject's parent/guardian signs informed consent until the last study visit.
[7] The subject's parent/legal guardian will be trained with regard to the correct instillation of eye drops without using study drug prior to their administration of the initial dose.

5.2 Study Endpoints

5.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the mean grade of anterior chamber inflammation (ACI) in the study eye at Visit 5 (Postoperative Day 14). The ACI grade will be determined using either slit lamp biomicroscopy or a penlight with handheld magnification. The grading from each method will be combined into one ACI grade to be used as the primary endpoint, derived using the following table:

ACI Grade	Slit lamp	Penlight with handheld magnifying 20 diopter lens
0 = None	Grades 0 cells and flare	Grade 0
1 = Mild	Maximum of cells and flare Grade is 1	Grade 1
2 = Moderate	Maximum of cells and flare Grade is 2	Grade 2
3 = Severe	Maximum of cells and flare Grade is 3	Grade 3
4 = Very Severe	Maximum of cells and flare Grade is 4	Grade 4

5.2.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include the following:

- Mean grade of ACI at Visits 4 and 6 (Postoperative Days 7 and 28)
- Proportion of subjects with Grade 0, Grade 1, Grade 2, Grade 3, and Grade 4 converted ACI at each visit (Postoperative Days 7, 14, and 28)
- Presence/absence and total area, if present, of synechiae at each visit (Postoperative Days 7, 14, and 28)
- Presence/absence and total number, if present, of precipitates on the implant and cornea at each visit (Postoperative Days 7, 14, and 28)

5.2.3 Safety Endpoints

The safety endpoints include the following:

- Incidence of overall and specific adverse events (AEs)
- Type and incidence of AEs at each visit
- Change in IOP from baseline (Visit 2, Surgery/Randomization) to each visit
- Greatest IOP change from baseline - including the measurement at Visit 3 (Postoperative Day 1)
- Greatest IOP change from baseline - excluding the measurement at Visit 3 (Postoperative Day 1)
- Ocular signs (biomicroscopic examination of the lids, conjunctiva, cornea, anterior chamber without pupil dilation) at each visit

5.2.4 Tolerability Endpoints

The tolerability endpoint is as follows:

- Ocular symptoms (photophobia) at each visit

5.3 Statistical Hypotheses

The test for the non-inferiority of LE Ophthalmic Gel, 0.5% to Prednisolone Acetate Ophthalmic Suspension, 1% will be based on the following one-sided null hypothesis (H_0) and alternative hypothesis (H_a):

$$H_0: \mu_{LE} - \mu_{PR} \geq 0.35 \text{ versus } H_a: \mu_{LE} - \mu_{PR} < 0.35,$$

where μ_{LE} and μ_{PR} are the mean grade of ACI at Visit 5 (Postoperative Day 14) for LE Ophthalmic Gel, 0.5% and Prednisolone Acetate Ophthalmic Suspension, 1% treatment groups, respectively.

5.4 Sample Size

The planned sample size of 120 completed subjects (60 subjects per treatment group) yields 98% power to detect non-inferiority of LE Ophthalmic Gel, 0.5% to Prednisolone Acetate Ophthalmic Suspension, 1%. This sample size assumes a common standard deviation of 0.47, a two-sided alpha=0.05, a non-inferiority margin of 0.35 and an expected difference of 0 for the difference in means between treatment groups using ACI at Visit 5 (Postoperative Day 14). Assuming a subject dropout rate (including the initiation of rescue medication) of 12%, approximately 140 subjects will be randomized, of which at least 60 subjects will be in the age group 0-3 years as per the FDA's Written Request.

The power and sample size calculations were done using nQuery Advisor version 7.0.

5.5 Randomization and Masking

A total of approximately 140 subjects from ages 0-11 will be randomized at Visit 2 (Day 0 to receive LE Ophthalmic Gel, 0.5% or Prednisolone Acetate Ophthalmic Suspension, 1% in a 1:1 ratio. The subgroup age 0-3 years will consist of at least 60 subjects.

The final randomization list will be created prior to study enrollment by an unmasked statistician not otherwise involved in the trial. Each randomization number will correspond to a treatment group assignment. The Investigator and Sponsor personnel involved in the conduct of the study will be fully masked to the study medication. Designees at each study site will be able to view both test and comparator bottles and are therefore considered unmasked, although they will not have access to the randomization codes.

The randomization code can be broken in an emergency situation before the database lock where knowledge of the study treatment is critical to subject safety.

5.6 Study Sample

Approximately 140 subjects will be enrolled in this double-masked, parallel-group, active-controlled study at approximately 30 investigative sites in the United States (US), European Union (EU), and Asia Pacific (AP).

5.6.1 Inclusion Criteria

Subjects must meet all the inclusion criteria listed in Section 3.2.1.1 of the clinical trial protocol.

5.6.2 Exclusion Criteria

Subjects have to meet (ie, respond "NO" to) all the exclusion criteria listed in Section 3.2.1.2 of the clinical trial protocol.

5.7 Procedures for Discontinuing Treatment and Removal of Subjects from Study

A subject CAN be discontinued (at the discretion of the Investigator, the Sponsor, and/or the Institutional Review Board/Ethics Committee) prior to the final study visit for any of several reasons, including, but not limited to:

- A serious adverse event (SAE) occurring during the course of the study, which precludes continued treatment or follow-up
- The subject's parent/legally authorized representative not following required study procedures

A subject HAS TO be discontinued prior to the final study visit for any of the following reasons:

- Voluntary withdrawal
- Onset of menarche during the study
- Death
- Investigator decision that it is not in the best medical interest of the subject to continue participation in the investigation
- Requires rescue medication

Adverse events and reasons for withdrawal and discontinuation will be documented appropriately according to the protocol. The assessments scheduled for Visit 8 (Postoperative Day 90) should be performed at this early termination visit. Any randomized subject discontinued from the study will not be replaced.

5.8 Test Article/Comparator Product

Loteprednol Etabonate Ophthalmic Gel, 0.5%, contains the active ingredient loteprednol etabonate 0.5% and the preservative benzalkonium chloride (BAK), 0.003%. It also contains the inactive ingredients glycerin, propylene glycol, sodium chloride,

polycarbophil, sodium hydroxide, tyloxapol, edetate disodium dihydrate, boric acid, and water for injection.

Prednisolone Acetate Ophthalmic Suspension, 1% contains the active ingredient prednisolone acetate 1% and the preservative BAK, 0.004%. It also contains the inactive ingredients boric acid, edetate disodium, hypromellose, polysorbate 80, purified water, sodium bisulfite, sodium chloride, and sodium citrate. The pH during its shelf life ranges from 5.0 - 6.0.

5.8.1 Selection and Timing of Dose

The subject will receive the first dose of study drug by the unmasked designee at the end of the surgery. Either the unmasked designee or the subject's parent/legal guardian will then administer 1 to 2 drops of study drug to the lower cul-de-sac of the study eye once in the evening on the day of surgery and then QID, at approximately 4 hour intervals, beginning on the morning after surgery. QID dosing will continue until postoperative day 14, including dosing at appropriate time intervals on the day of a visit. Dosing of both test articles was subsequently adjusted as described in Section 5.9.

5.9 Dose Adjustment/Modifications

Treatment will be tapered from QID to BID during the interval between postoperative days 15 and 21. Treatment will be further tapered to QD from postoperative day 22 until day 28, with the last dose being administered on the day prior to Visit 6 (Postoperative Day 28).

5.10 Treatment Compliance Follow-up

In order to assess compliance of treatment administration, subject/subject's parent/legal guardian will be instructed to record the date and time of each study drug administration on a diary provided by the Sponsor.

6 General Statistical Considerations

All statistical analyses will be conducted using SAS Version 9.4 or higher.

Continuous data will be summarized using descriptive statistics: n, mean, standard deviation, median, minimum, and maximum. Means and medians will be presented to 1 more decimal place than the recorded data. Standard deviations will be presented to 2 more decimal places than the recorded data. Minimum and maximum values will be presented using the same number of decimal places as the recorded data. Categorical data will be summarized using counts for each category and corresponding percentages. Percentages will be presented to 1 decimal place. Confidence intervals will be presented using the same number of decimal places as the parameter (i.e. mean).

All statistical analyses will generally include summaries by treatment group or by treatment group and scheduled time point, as appropriate.

In general, the baseline value for a variable is defined as the last observation prior to the first dose of double masked study medication (Day 0), including the screening value, if necessary.

Study Day 0 is defined as the date on which a subject was randomized and took the first dose of double masked study medication. Other study days are defined relative to the Study Day 0 as Dose Date – Day 0 date + 1. The visit window for Day 7 is ±2, for Day 14 is ±3, for Day 28, 42, is ±7, and for Day 90 is ±14.

6.1 Analysis Populations

6.1.1 Intent to Treat (ITT)

Intent-to-Treat (ITT) population: includes all subjects who were randomized and have at least one post-treatment assessment. Analysis of the ITT population will be used for primary efficacy analyses and will be performed for all efficacy endpoints, analyzing subjects under the treatment to which they were randomized.

6.1.2 Per Protocol (PP)

Per Protocol (PP) population: includes all of the subjects in the ITT population that remained in the study through Visit 5 (Postoperative Day 14) and who did not deviate from the protocol in any way likely to seriously affect the primary outcome of the study. Analyses using the PP population will be used to supplement the ITT analysis, analyzing subjects according to the treatment received.

6.1.3 Safety (SAF)

Safety analysis population: includes all participants who received at least one dose of study drug.
All subjects in the Safety analysis population will be analyzed according to the treatment received. All safety and tolerability analyses will be based on the Safety analysis population.

6.2 Handling of Missing Data

For the primary efficacy endpoint analyzed using the ITT population, missing data and data from subjects placed on rescue medication prior to Day 14 will be analyzed using

the last observation carried forward (LOCF). For the PP analysis, missing data and data from subjects placed on rescue medication will not be imputed.

Data from unscheduled/repeated visits will be presented in listings and will be included in safety summaries for considering the worst-case scenario.

6.3 Changes in the Planned Analysis

Change from protocol: Investigation site is added as a covariate in the primary analysis model, and the model was changed from a one-way ANOVA to an ANCOVA model. Any deviations from this statistical analysis plan will be documented in the final clinical study report.

7 Subject Disposition

A disposition table of subjects will include the number and percentage of subjects in each of the following categories:

- Subjects randomized (ITT analysis population)
- Subjects treated (Safety analysis population)
- Subjects in the PP analysis population

Within each of the previous categories, the number and percentage of subjects who completed and discontinued from the study will be summarized.

The reasons for study discontinuation will also be summarized. The reason for discontinuation may include any of the following:

- Withdrew consent
- Lost to follow-up
- Administrative issue
- Adverse event
- Rescue Therapy
- Failure to follow required study procedures
- Investigator decision that it is not in the best medical interest of the subject
- Onset of menarche
- Other

Only 1 reason (primary) for study discontinuation will be recorded for each subject.

A listing will present data concerning subject disposition and other reasons for discontinuation

7.1 Protocol Deviations

The date of and reason for protocol deviations will be documented in all cases. Major protocol deviations will be finalized before the database lock. Major protocol deviations will be summarized. A listing of all protocol deviations will be presented.

8 Demographics and Baseline Characteristics

8.1 Demographics

Demographic characteristics including race, ethnicity, gender, iris color, and age will be summarized by treatment group for the ITT, PP and SAF. Age (≤ 3 years, > 3 years), race, ethnicity, iris color, source of breast milk, and gender will be summarized as categorical variables, while age will also be summarized as a continuous variable. All percentages will be based on the number of randomized subjects. Comparability of baseline variables will be tested using two-sided t-test or Chi-square test, as appropriate.

8.2 Non-Ocular and Ocular Medical History

Non-ocular medical history will be listed by subject and summarized as categorical variables at the subject and event level by system organ class and preferred term for each treatment group. Ocular history will be listed and summarized similarly for study and fellow eyes separately.

8.4 Inclusion and Exclusion Criteria

A listing of inclusion and exclusion criteria along with date of informed consent will be listed by subject.

9 Treatments and Medications

9.1 Prior and Concomitant Medications

All medications will be coded using the World Health Organization (WHO) drug dictionary version 1Q2010. All non-study drugs (including prescribed and over the counter [OTC] medications) used within 30 days prior to study entry and all non-study drugs used during the course of the study will be collected on the eCRF.

Concomitant medication use will be summarized by the number and percentage of subjects taking each medication. Medications taken prior to study drug will be presented in a listing. Rescue medication will be listed and summarized, if appropriate.

9.2 Study Treatments

9.2.1 Extent of Exposure

Extent of exposure is defined as the total number of days from the first dose date to the last dose date, as recorded at the randomization study visit and the study exit eCRF page. Study drug exposure will be calculated based on subject diary data.

The extent of exposure and study drug exposure will be summarized in a table by summary statistics including the mean, standard deviation, median, minimum, and maximum exposure.

9.2.2 Treatment Compliance

Study drug compliance will be calculated for each subject by taking into account whether a subject takes all doses of study drug as instructed. Compliance will be based solely on the subject diaries. The study drug compliance rate will be presented overall, at Visit 4, Visit 5 and Visit 6. The study drug compliance rate for Visit 5 will be calculated by dividing the total number of dosingl recorded in the diary for the subject for that period by the total number of days times 4 and then multiplying by 100. The first day of dosing will be ignored entirely, since subjects may be compliant with any number of doses.

The overall study drug compliance rate will be calculated by dividing the total number of dosing recorded in the diary for a subject across the entire treatment period by the total number of days times 4 for days ≤ 14, times 2 for days between days 15 and 21 and times 1 for days between 22 and 28 and then multiplying by 100. The first day of dosing will be ignored entirely, since subjects may be compliant with any number of doses. The number and percentage of subjects in each of the following compliance rate categories will also be reported: (≤50%, 51-60%, 61-70%, 71-80%, 81-120%, and >120%). Percentages will be calculated out of the number of subjects who returned diaries from that dosing period. The number and percentage of subjects in each compliance rate category will be presented overall, at Visit 4, Visit 5 and Visit 6.

10 Statistical Analyses

All efficacy analyses will use a 2-sided alpha = 0.05 test unless otherwise stated. No adjustments will be made for multiplicity testing.

Analyses will be performed on the ITT and PP analysis set for both the primary efficacy endpoint and secondary efficacy endpoints. The safety analyses will be performed on the SAF.

All continuous efficacy endpoints will be summarized graphically by treatment group displaying the mean and corresponding standard errors at each time point for the primary efficacy endpoint or line graphs of the continuous secondary efficacy endpoints over scheduled time.

10.1 Primary Efficacy Analysis

The primary efficacy analysis will be based on the ITT population with missing data imputed using the last observation carried forward (LOCF) method and the primary endpoint will be mean grade of ACI at Visit 5 (Postoperative Day 14). The mean grade of ACI at Visit 5 (Postoperative Day 14) will be analyzed using an ANCOVA model with treatment as a classification variable and investigational site as a covariate.

The least squares mean for each treatment group, the difference in the least squares mean between the 2 treatment groups (LE Gel minus Pred Forte), and the 2-sided 95% confidence interval for the difference will be presented. The null hypothesis will be rejected and non-inferiority established if the upper limit of the confidence interval is less than 0.35.

To support the interpretation of the primary analysis, the analyses above will be repeated for the PP population; no imputation will be conducted for missing data or for subjects placed on rescue medication for the PP analysis. Any discrepancy between the ITT and PP analyses will be explained.

10.2 Secondary Efficacy Analysis

All secondary analyses will be based on the ITT and PP.

As a secondary analysis, the analysis of the observed mean grade of ACI will be repeated as above for Visits 4 and 6 (Postoperative Days 7 and 28, respectively).

Additional secondary analyses include:

- The proportion of subjects with ACI of Grade 0, Grade 1, Grade 2, Grade 3, and Grade 4 for each visit (Postoperative Days 7, 14, and 28)
- The proportion of subjects with presence/absence and total area, if present, of synechiae in the study eye for each visit (Postoperative Days 7, 14, and 28)
- The proportion of subjects with presence/absence and total number, if present, of precipitates on the implant and cornea in the study eye at each visit (Postoperative Days 7, 14, and 28)

For each of the above endpoints, treatment groups will be compared using the Pearson Chi-squared test or Fisher's exact test as appropriate. Differences between the

proportions of treatment groups and 95% confidence interval about the differences will be presented.

10.3 Other Analysis

Subgroup analyses will be performed for ACI and anterior chamber cells, anterior chamber flare as appropriate by method of assessment (slit lamp versus penlight with handheld magnifying 20 diopter lens), country (region), age group, intraocular lens (IOL) implantation, and iris color.

10.4 Safety Analysis

Safety analyses will be based on the SAF. The SAF will include all subjects who are confirmed to have received the study drug. All subjects in the SAF will be analyzed according to the treatment received.

10.4.1 Treatment Emergent Adverse Events

Adverse events (AEs) are defined in Section 6.1 of the protocol and initiating collection of AEs is defined in Section 5.1.2 of the protocol. Adverse events will be coded using MedDRA dictionary version 13.0.

All AEs collected with start dates following the first administration of study drug or that worsen following the first administration of study drug are considered treatment-emergent adverse events (TEAE).

Adverse events with unknown severity will be counted as severe. Adverse events with unknown relationship to study drug will be counted as related to study drug. Adverse events with partial dates will have their start dates imputed. If the partial date is consistent with the first day of treatment, it will be imputed with this value; otherwise it will be imputed as the earliest possible date consistent with the partial data (first day of month/ year). If a start or end date are completely missing, then the date will be imputed with the dates of the first or last date of treatment, respectively.

10.4.1.1 Incidence of Treatment-Emergent Adverse Events

Treatment emergent non-ocular AEs will be summarized using discrete summaries at the subject and event level by system organ class and preferred term for each treatment group. Treatment emergent ocular AEs will be summarized for treated study eyes and fellow eyes separately.

10.4.1.2 Relationship of Treatment-Emergent Adverse Events to Study Drug

Treatment emergent AEs will be summarized by relationship to study drug. Relationship of adverse events to study drug may be 'Not Related' or 'Related'. Adverse events that are missing relationship will be presented in the summary table as "Related" but will be presented in the data listing with a missing relationship. Percentages will be calculated out of the number of subjects in the Safety sample.

10.4.1.3 Severity of Treatment-Emergent Adverse Events

A summary of TEAEs by severity will be presented in a table. The severity that will be presented represents the most extreme severity captured. Adverse events will be assessed by the Investigator as "Mild," "Moderate," or "Severe." In the AE severity table, if a subject reported multiple occurrences of the same AE, only the most severe will be presented. Adverse events that are missing severity will be presented on tables as "Severe" but will be presented in the data listing with a missing severity. Percentages will be calculated out of the number of subjects in the Safety sample.

10.4.1.4 Seriousness of Adverse Events

Serious adverse events (SAEs) are defined in Section 6.2 of the protocol. A listing and table of SAEs will be presented.

10.4.1.5 Treatment-Emergent Adverse Events Leading to Discontinuation

All TEAEs resulting in study discontinuation will be presented in a listing.

10.4.1.6 Treatment-Emergent Adverse Events Related to Study Drug

All TEAEs assessed as related to the study drug will be presented with time to onset and outcome in a listing by treatment group.

10.4.1.7 Death

All subject deaths during this study will be collected and presented in a listing. The information presented will include date of death, days on study, cause of death, and relationship of death to study drug.

10.4.2 Surgical Intervention

Surgical procedure data will be presented in a listing.

10.4.3 Other Safety Data

10.4.3.1 Biomicroscopy / Fundoscopy

The slit lamp/penlight with magnifying lens biomicroscopy will be performed at all visits. The biomicroscopy parameters will include:

- Anterior chamber cells or ACI
- Anterior chamber flare or ACI
- Ciliary flush
- Chemosis
- Ocular discharge
- Ocular tearing
- Bulbar conjunctival injection
- Corneal edema
- Hyphema
- Hypopyon
- Posterior synechiae
- Precipitates

Biomicroscopy findings will be summarized at each visit and for the worst case on treatment by subject and parameter. Incidence of treatment-emergent biomicroscopy findingswill be tested using the Pearson Chi-squared Test or Fisher's Exact Test as applicable.

The fundoscopy parameters will include:

- Posterior Pole
- Optic Nerve
- Cup/Disc Ratio

Fundoscopy measures will be summarized by visit. Incidence of treatment-emergent fundoscopy findings will be tested using a Pearson Chi-squared Test or Fisher's Exact Test, if applicable.

10.4.3.2 Visual Acuity

Visual Acuity (VA) method will be summarized. VA assessments will be summarized at each visit as a categorical variable (ie: 20/20, 20/40, or fix and follow etc) and as a line change from baseline as applicable. Worst line change from baseline will also be presented. Subjects presenting a line change of >2 lines will be tested using a Pearson Chi-squared Test or Fisher's Exact Test as applicable.

10.4.3.3 Intraocular Pressure

Intraocular pressure (IOP) will be summarized at each visit and worst case on treatment for each subject using both continuous summaries (including change from baseline) and discrete summaries. Discrete summaries will include:

- Change in IOP from baseline (Visit 2) to each visit
- The proportion of subjects with change in IOP from baseline ≥5 and ≥10 mm Hg
- The proportion of subjects with treatment-emergent IOP ≥25 mm Hg
- IOP at each visit categorized into: ≤ 4, 5 to 7, 8 to 12, 13 to 16, 17 to 20, 20 to 25, and ≥25
- Greatest IOP change from baseline - including the measurement at Visit 3 (Postoperative Day 1)
- Greatest IOP change from baseline - excluding the measurement at Visit 3 (Postoperative Day 1)
- Change from baseline in IOP at each visit categorized into: ≤-5, -4 to 0, 1 to 4, 5 to 9, 10 to 14, and ≥15

10.4.3.4 Ocular Symptoms

Ocular symptom/tolerability (photophobia) data will be summarized by visit and treatment group. The listing will use the SAF population with actual treatment received.

11 Interim Analysis

In order to provide the primary CSR for FDA review, an interim analysis will be performed for all subjects who exited (not completed, but exited, including discontinued subjects) on or before 28Feb2017. This interim analysis will contain all tables, listings and figures as the final analysis. There will be no statistical adjustments to the study-wide alpha level for the interim analysis.

12 Revision History

12.1 Revision 01

This revision was issued following protocol amendment 6, issued on 22MAY2013.
Summary of changes from the prior SAP version: 1.0, dated 04June2012.

Section #	Description of Change	Rationale
All	Administrative changes	To provide clarity and consistency to the SAP text

Section #	Description of Change	Rationale
3	Changed phase number from 3b to 4	Change based on protocol amendment 6
5.1	Changed subject number from 158 to 140; 79 to 60 and 40 to 30.	Change based on protocol amendment 6
5.1	Changed description of study duration as follows: "Study duration will be approximately 12-18 11-19 weeks…"	Change based on protocol amendment 6
5.1	Deleted the "Design Schematic"	Change based on protocol amendment 6
5.1	Updated the schedule of visits and parameters	Change based on protocol amendment 6
5.2.1	Changed Visit 4 to Visit 5, and Day 7 to Day 14	Change based on protocol amendment 6
5.2.1	Added "The ACI grade will be determined using either slit lamp biomicroscopy or a penlight with handheld magnification. The grading from each method will be combined into one ACI grade to be used as the primary endpoint"	The original SAP is not clear about the ACI grade calculation.
5.2.2	Changed Visit 5 to Visit 4, and Day 14 to Day 7	Change based on protocol amendment 6
5.2.2	Changed Day 29 to Day 28	Change based on protocol amendment 6
5.3	Changed the non-inferiority margin from 0.5 to 0.35	Change based on protocol amendment 6
5.3	Changed Visit 4-Day 7 to Visit 5-Day 14	Change based on protocol amendment 6
5.4	Changed the sample size calculation to be the same as the protocol	Change based on protocol amendment 6
5.5	Changed subject number from 158 to 140 Changed: the subgroup age 0-3 years will consist of at least 60 subjects. ~~The subgroup age 0-3 years will be randomized in approximately equal proportion.~~	Change based on protocol amendment 6
5.6	Changed subject number from 158 to 140 Added Asia Pacific (AP)	Change based on protocol amendment 6
5.7	Added onset of menarche during the study	Change based on protocol amendment 6
5.7	Changed: The assessments scheduled for Visit 8 (Postoperative Day 90) should be performed at	Change based on protocol amendment 6

Section #	Description of Change	Rationale
	this early termination visit. ~~Assessments scheduled for the planned Visit will be performed at the early discontinuation visit~~	
5.9	Changed Day 29 to Day 28	Change based on protocol amendment 6
6	Changed version 9.1 to version 9.4	SDC will use the latest SAS version
6	Changed: The visit window for Day 7 is ±2, ~~and~~ for Day 14 is ±3~~1~~, ~~and the visit window~~ for Days 2~~9~~8, 42, is ~~and 90 is~~ ±7~~3~~, and for Day 90 is ±14.	Change based on protocol amendment 6
6.1.1	Changed the "secondary" to "primary"	Change based on protocol amendment 6
6.1.2	Changed Visit 4-Day 7 to Visit 5-Day 14	Change based on protocol amendment 6
6.1.2	Changed: Analyses ~~on the~~ using the PP set will be used ~~for the primary efficacy analysis and will be performed~~ to supplement the ITT analysis, analyzing subjects according to the treatment received.~~or the primary and secondary efficacy endpoint, analyzing subjects according to the treatment received.~~	Change based on protocol amendment 6
6.2	Deleted: ~~Subjects with missing data or with rescue medication prior to Day 7 will be excluded from the primary PP analysis.~~	Change based on protocol amendment 6
6.2	Changed Day 7 to Day 14	Change based on protocol amendment 6
6.2	Changed: For the ~~secondary efficacy endpoints analyzed using the ITT set~~ PP analysis, missing data and data from subjects placed on rescue medication ~~prior to the visit being summarized~~ will not be imputed ~~as LOCF and will also be summarized as missing~~.	Change based on protocol amendment 6
8.1	Changed analysis of variance (ANOVA) to two-sided t-test	Change based on protocol amendment 6
9.2.2	Changed: Visit 4-Day 7 to Visit 5-Day 14	Change based on protocol amendment 6
10.1	Changed Visit 4-Day 7 to Visit 5-Day 14	Change based on protocol amendment 6
10.1	Changed the non-inferiority margin from 0.5 to 0.35	Change based on protocol amendment 6
10.1	Change the primary endpoint into ITT with LOCF	Change based on protocol

Section #	Description of Change	Rationale
		amendment 6
10.1	Delete the pattern mixture model part	Change based on protocol amendment 6
10.1	Add “and investigational site as a covariate.”	Site might have significant impact on the primary endpoint.
10.2	Changed Visit 5 to Visit 4, and Day 14 to Day 7	Change based on protocol amendment 6
10.2	Changed Day 29 to Day 28	Change based on protocol amendment 6
10.2	Removed the whole ANCOVA model section	The baseline measurements on Visit 2 (Day 0) were taken prior to the surgery, which means the results should all be negative (no ACI). So it’s not meaningful to use baseline as a covariate in this case
10.2	Added “in the study eye” in the second and third bulletins	To clarify that these two tables are only summarized for study eye
10.4.1.1	Added “Treatment-Emergent”	Sponsor requested to clarify
10.4.1.2	Added “Treatment-Emergent”	Sponsor requested to clarify
10.4.1.3	Added “Treatment-Emergent”	Sponsor requested to clarify
10.4.1.5	Added “Treatment-Emergent”	Sponsor requested to clarify
10.4.1.6	Added “Treatment-Emergent”	Sponsor requested to clarify