Statistical Analysis Plan

Study code	[redacted]
Version	Final
Date	Sep11, 2018

A RANDOMIZED, MULTICENTER, DOUBLE MASKED, PLACEBO CONTROLLED, PARALLEL GROUP, BIOEQUIVALENCE STUDY TO EVALUATE THE CLINICAL EQUIVALENCE AND SAFETY OF NEPAFENAC 0.3% OPHTHALMIC SUSPENSION [redacted] FOR ACTAVIS LLC) WITH ILEVRO™ (NEPAFENAC OPHTHALMIC SUSPENSION), 0.3% OF ALCON LABORATORIES, INC. FOR THE TREATMENT OF PAIN AND INFLAMMATION ASSOCIATED WITH CATARACT SURGERY

Study Statistician

[redacted]

Sponsor Representative

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
BMI	Body Mass Index
CRO	Clinical Research Organization
DOB	Date of Birth
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
HEENT	Head, Eyes, Ears, Nose, Throat
IOP	Intraocular Pressure
IP	Investigational Product
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
PP	Per Protocol
PT	Preferred Term
TEAE	Treatment Emergent Adverse Event
SAE	Serious Adverse Event
SOC	System Organ Class

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol "A randomized, multicenter, double masked, placebo controlled, parallel group, bioequivalence study to evaluate the clinical equivalence and safety of Nepafenac 0.3% ophthalmic suspension [redacted] Actavis LLC) with Ilevro™ (Nepafenac ophthalmic suspension), 0.3% of Alcon Laboratories, Inc. for the treatment of pain and inflammation associated with cataract surgery", version 2.0, amendment 2.0 dated June 25, 2018.

This study is designed to determine clinical equivalence of an ophthalmic suspension in order to facilitate the registration of a generic version of Nepafenac 0.3% suspension. The reference listed drug for this suspension is Ilevro™ (Nepafenac Ophthalmic Suspension 0.3%). This study will be conducted in male and female subjects with cataract.

This document will give a description of the planned methods of the analysis.

2. OBJECTIVES

The objectives of this study are:

- To demonstrate the clinical equivalence of Nepafenac 0.3 % ophthalmic suspension ([redacted] Actavis LLC) with Ilevro™ (Nepafenac ophthalmic suspension), 0.3 % of Alcon Laboratories, Inc. for the treatment of pain and inflammation associated with cataract surgery.

- To demonstrate the superiority of the efficacy of the test and reference products over the placebo control in the treatment of pain and inflammation associated with cataract surgery.

3. STUDY OVERVIEW

3.1 Study Design

Approximately 450 subjects [redacted] will be enrolled and randomized in this investigational study. [redacted]

One drop of the suspension should be instilled into the affected eye one-time daily, beginning a day prior to the planned cataract surgery, on the day of the cataract surgery, and for 14 days thereafter. On the day of cataract surgery (day 0) a drop should be added 30-120 minutes prior to the surgery and an additional drop will be administered following cataract surgery prior to the subject leaving the surgery center. The study is designed to be only monocular (only one eye per subject).

The dose and mode of treatment chosen in this study is the dosage approved by US FDA for the treatment of pain and inflammation associated with cataract surgery.

The study subjects will undergo clinical evaluations throughout the study in order to assess efficacy and safety at the following visits:

- Visit 1: Day -21 to Day -1 (Screening/Baseline/Randomization Visit)
- Visit 2: Day 0 (The Day of Cataract Surgery)
- Visit 3: Day 1 (One Day After the Cataract Surgery)
- Visit 4: Day 7± 2 Days (Follow up Visit)
- Visit 5: Day 14 ±2 Days (End of Study Visit/Early Discontinuation)

An Unscheduled Visit is allowed at any time, for any reason, if in the Investigator's opinion it is warranted.

If the Investigator determines that the study subject's condition has worsened to the degree that it is unsafe for continuation in the study, the study subject may be discontinued and will be evaluated as a treatment failure.

3.2 Sample Size

[redacted]

Thus, approximately 450 subjects [redacted] will be enrolled and randomized [redacted]

3.3 Randomization Procedures

Subjects will be randomly assigned [redacted] to receive the Test product or the Reference Product or the Placebo control, respectively. The randomization schedule for this study will be generated by a third-party vendor of the CRO such that a non-study-assigned independent expert will allocate the subjects to one of the three treatment arms using a computer generated automated process i.e. Interactive Web Response System (IWRS). A sealed copy of the randomization scheme will be retained at the study site and should be available to regulatory authority inspectors at the time of site inspection to allow for verification of the treatment identity of each subject.

4. STUDY ENDPOINTS/OUTCOMES

Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with cure at Day 14 defined as a score of 0 for aqueous cells, a score of 0 for aqueous flare and a score of no more than 3 for pain.

Safety Endpoints

The safety endpoints include:

- The incidence of treatment emergent adverse events.
- Ocular parameters (visual acuity, intraocular pressure measurement, slit lamp evaluation and dilated fundus examination).

5. HYPOTHESES TESTING

Hypothesis of Equivalence

A two-sided, continuity-corrected, 90% confidence interval on the Test-to-Reference difference for the proportion of subjects with cure will be constructed.

Bioequivalence will be established if the 90% confidence interval for the difference is contained within the interval [-0.20, +0.20].

Hypothesis of Superiority

The null hypothesis to be tested is that there is no difference in the proportions of subjects with cure. The evaluation of superiority will be conducted separately for the Test treatment versus the Placebo treatment and for the Reference treatment versus the Placebo treatment. The analysis will be conducted using two-sided, $\alpha = 0.05$, Fisher's exact test.

Superiority will be established if the proportion of cure for each active treatment is greater than, and statistically different from, that of the Placebo.

6. ANALYSIS SUBSETS

6.1 Safety Population

The safety population includes any subject who was randomized into the study and has evidence of usage of at least one dose of IP according to subject's diary or eCRF.

6.2 Modified Intent to Treat Population (mITT Population)

The mITT population includes all randomized subjects who met all inclusion/exclusion criteria and return for at least one post-operative evaluation visit. This population will be used while testing the superiority.

6.3 Per Protocol Population (PP Population)

The PP population includes all randomized subjects who:

- Met all the inclusion and none of the exclusion criteria;
- [redacted]

For the purpose of determining the PP status of the subject, a "protocol deviations that would affect the treatment evaluation" is any of the major protocol deviations as defined in section 7.5.

The PP population will be used for testing the clinical equivalence.

7. STATISTICAL METHODS OF ANALYSIS

7.1 General Principles

The statistical analyses will be performed by [redacted] under the direction of the Sponsor, Actavis LLC, using SAS Version 9.4 (or higher). All tables, figures, and listings will be produced in the landscape format.

In general, all data will be listed by treatment group, subject and visit/time point where appropriate. The summary tables will also be stratified by, or have columns corresponding to, treatment groups.

All subjects will be identified by their unique subject numbers.

The total number of subjects in the study group (N) under the stated population will be displayed in the header of summary tables.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise specified, descriptive statistics will include number of subjects, mean, standard deviation, minimum, median, and maximum. The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean and median will be presented to one more decimal place than the original data. The standard deviation will be presented to two more decimal places than the original data. The number of missing observations will be presented only if non-zero.

In summary tables of categorical variables, counts, and percentages will be used. The count [n] indicates the actual number of subjects in a particular category, which should always be less than or equal to the total number of subjects in the respective study group with known (non-missing) category [M]. Percentage will be obtained by: % = n/M*100. Unless otherwise stated, all percentages will be expressed to one decimal place.

All statistical tests will be two-sided at a significance level of $\alpha = 0.05$, unless otherwise indicated. No adjustment will be made for multiplicity.

The eye on which the cataract surgery is performed will be referred to as the study eye, and the other eye as the non-study eye. Ocular safety information will be presented separately for the study eye and non-study eye. Efficacy will be assessed for the study eye only.

Baseline will be defined as the last assessment obtained prior to the first dose of the study drug, unless otherwise specified.

Relative days will be calculated relative to date of first dose of study medication. Relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days).

For assessment on or after the day of first dose of study drug:

Relative Day = Date of Assessment – Date of First Dose of study Drug+1.

For assessment before the day of first dose of study drug:

Relative Day = Date of Assessment – Date of First Dose of study Drug.

Note: relative days are different from protocol-specified visit names; Day -1 visit will typically correspond to Day 1 relative to the first dose of the study drug.

All dates will be displayed in DDMMMYYYY format.

7.1.1 First Dose of the Study Drug

The dose of the study drug taken on the day prior to surgery will count as the first dose of the study drug.

It is possible that a subject is scheduled to have their surgery on a certain date, and according to the protocol, they take a drop of the study drug one day prior, however, then the surgery is rescheduled to a later date. In this case the subject would keep the IP, stop taking it, and apply a new drop before the new scheduled date of surgery. The very first drop taken prior to the date of cancelled surgery will count as the first dose of the study drug only for the purposes of determining the treatment-emergent status of AEs. It will not count as the first dose of the study drug for any other purposes, including, but not limited, to the following:

1. definition of baseline;
2. reference date for calculation of relative days;
3. calculation of study drug exposure and compliance.

Instead, the dose taken prior to the actual surgery will be considered as the first dose of the study drug.

7.2 Subject Disposition

The number of subjects screened in the study, randomized to treatment, included in the Safety, PP, mITT populations, prematurely discontinued from the study (along with the reasons for discontinuation) will be calculated. The percentages will be based on the number of subjects randomized to each treatment group. Percentages for discontinuation reasons will be based on the sub-population of subjects who discontinued from the study.

Number and percentage of subjects enrolled by site will be tabulated for all enrolled subjects, Safety, mITT, and PP populations.

7.3 Demographic and Baseline Characteristics

Demographic characteristics will include:

- age;
- gender;
- race;
- ethnicity;

Baseline characteristics include:

- height, weight, body mass index (BMI)
- iris color
- aqueous cells grade for the study eye
- aqueous flare grade for the study eye
- ocular pain grade for the study eye

Descriptive statistics will be presented for age (years), height, weight and BMI. Frequency counts and percentages will be presented for race, ethnicity, iris color and baseline grades. Height will be reported in centimeters and weight in kilograms.

Age will be derived from Informed Consent Signed Date (INFCSD) and Date of Birth (DOB) as the number of whole years between those two dates.

Demographic and baseline characteristics will be evaluated for comparability across treatment groups in the following manner. Continuous variables (age, height, weight, BMI) will be analyzed with an ANOVA with factors of treatment and investigational site. Overall p-value for the global null hypothesis of all groups being equal will be displayed. Categorical variables (gender, ethnicity, race, iris color, baseline grades) will be analyzed with a Cochran-Mantel-Haenszel general association test, stratified by investigational site.

These analyses will be performed for Safety, mITT, and PP populations.

All parameters reported during screening or baseline phase (including informed consent information, inclusion/exclusion criteria, randomization information, method of contraception, etc.) will be presented in by-subject listings.

7.4 Medical History

Medical history will be summarized by MedDRA (version 20.1) System Organ Class (SOC) and Preferred Term for the safety population. Each subject will be counted once within each applicable SOC and Preferred Term. All medical history information collected on the eCRF will also be listed.

7.5 Protocol Deviations

Protocol deviations will be derived algorithmically (programmable) as well as reported by sites (observable). Each protocol deviation will be classified as minor or major. In the case there are differences in the programmable vs. observable protocol deviations, the programmable protocol deviation will take precedence. Specific deviation and their severity are defined in the separate Protocol Deviations List document.

All major protocol deviations will be summarized by deviation category and treatment group. This analysis will be performed for the Randomized set.

7.6 Cataract Surgery

All details of the surgery captured on the eCRF will be listed.

7.7 Efficacy Analyses

7.7.1 Analyses of Primary Endpoint

The primary efficacy endpoint is the proportion of subjects with cure at Visit 5 (end of the study on Day 14+/-2). A subject is defined as cure if they have a score of 0 for aqueous cells, a score of 0 for aqueous flare and a score of no more than 3 for pain in the study eye. A subject is defined as failure if they have a score of >0 for aqueous cells, or score of >0 for aqueous flare or a score of >3 for pain in the study eye.

[redacted]

The denominator for percentages will be the number of subjects with either cure or failure, i.e. subjects without a valid assessment will be excluded.

7.7.1.1 Analysis of clinical equivalence of test and reference treatments

A two-sided, continuity-corrected, 90% confidence interval on the Test-to-Reference difference for the proportion of subjects with cure will be constructed. Bioequivalence will be established if the 90% confidence interval for the difference is contained within the interval [-0.20, +0.20] for the PP population.

Analysis of bioequivalence will be performed on the PP population.

7.7.1.2 Analysis of superiority to placebo

The evaluation of superiority will be conducted separately for the Test treatment versus the Placebo treatment and for the Reference treatment versus the Placebo treatment, comparing the proportions of subjects with cure. The analysis will be conducted using two-sided Fisher's exact test.

Superiority will be established if the cure proportion for each active treatment is greater than, and statistically significantly different from ($p < 0.05$ for the Fisher's test) that of the Placebo for the mITT population. Analysis of superiority will be performed on the mITT population.

7.7.2 Analyses of Individual Efficacy Parameters

Aqueous cells, aqueous flare and ocular pain will be assessed at Visits 1, 3, 4 and 5. Aqueous cells will be assigned a grade from 0 (None) to 4 (Greater than 30 cells) (see section 11.2 for complete scale); aqueous flare a grade from 0 (No visible flare when compared with the normal eye) to 3 (Very dense flare) (see section 11.3 for complete scale). Ocular pain will be graded from 0 (None) to 5 (Severe) (see section 11.4 for complete scale).

Number and percentage of subject at each grade for aqueous cells, aqueous flare and ocular pain in the study eye will be tabulated by visit. This analysis will be performed for both mITT and PP populations.

7.8 Safety Analyses

7.8.1 Adverse Events

Adverse Events will be coded using the MedDRA, Version 20.1, AE coding system for purposes of summarization.

Only Treatment Emergent Events (TEAEs) will be used for the summary analysis. An AE will be considered as treatment-emergent if the time of onset is after the time of the first study drug administration or if it increased in severity during the study period. AEs with unknown start dates will be counted as treatment-emergent unless the AE resolution date is prior to the study drug start date. If the start date is partially missing, then month and year (when available) will be used to determine if the event occurred prior to or post dosing.

A TEAE is considered as treatment-related if it is recorded as Related on the eCRF. In case the relatedness was not assessed, the most conservative result – related – will be chosen for the analysis.

An overall summary will include, by treatment group and overall, the number of TEAEs and the number and percentage of subjects reporting at least 1 TEAE, as well as number of TEAEs in the following categories:

- Any TEAE,
- Treatment-related TEAE,
- Serious TEAE,
- TEAE leading to discontinuation of the study medication.

The following TEAE frequency tables will be prepared summarizing the number and percentage of subjects reporting at least one TEAE by MedDRA SOC and PT:

- All TEAEs,
- TEAEs by Severity,
- TEAEs by Relationship to Study Medication.

These AE summaries will be presented in alphabetical order of SOC and preferred terms.

Additionally, TEAEs will be summarized by the preferred terms in the descending order of frequency in the total treatment group. In this table a p-value from Fisher's exact test

comparing event rates between the Test and the Reference treatment groups will be provided for those preferred terms that have frequency > 1% in either Test or Reference group.

A subject experiencing the same AE multiple times will only be counted once for that preferred term. Similarly, if a subject experiences multiple AEs within the same system organ class, that subject will be counted only once in that system organ class. In summaries by severity and relationship each subject will be counted with the highest applicable severity and the closest applicable relationship.

All information pertaining to adverse events noted during the study will be listed by subject, detailing verbatim, preferred term, system organ class, start date, stop date, intensity, outcome, action taken, and causal relationship to the study drug. The adverse event onset will also be shown relative (in number of days) to the date of first administration of the study drug. In addition, the adverse event duration (if AE Stop Date is available) will be evaluated as below and presented (in number of days).

AE Duration = AE Stop Date – AE Start Date + 1

7.8.2 Laboratory Tests

The following laboratory tests will be performed at Visit 1 Screening and Visit 5 Day 14.

Serum Chemistry	ALT	AST	BUN
	Total Bilirubin	Glucose	Creatinine
Hematology	Hemoglobin	Total WBC count with differentials	
Urinalysis	Appearance	Specific Gravity	Protein
	pH	Microscopic examination	

If warranted, other tests or examinations may be performed at the discretion of the investigator.

Actual values and changes from baseline for laboratory test results will be summarized descriptively by visit and treatment group. Test results will be presented in conventional units.

Additionally, numeric Serum Chemistry, Hematology and Urinalysis results will be classified as Low (below the reference range), Normal (within the reference range) or High (above the reference range). Categorical Urinalysis results will be classified as Normal or Abnormal. Shifts among these categories between baseline and Visit 5 Day 14 will be provided.

All results will be listed.

7.8.3 Vital Signs

Vital signs, including systolic and diastolic blood pressure, pulse rate, respiratory rate and body temperature will be assessed at all study visits. Overall interpretation will be recorded as Normal, Abnormal Not Clinically Significant or Abnormal Clinically Significant.

Height and weight will be measured and BMI will be calculated at Visit 1 Screening and Visit 5 Day 14+/-2.

Actual values and changes from baseline for vital signs (including height, weight an BMI) will be summarized descriptively by visit and treatment group. Overall interpretation will be summarized categorically by visit and treatment group. All vital signs results (including height, weight and BMI) will be listed.

7.8.4 Physical Examination

Physical examination will be performed at Visit 1 Screening and Visit 5 Day 14+/-2. The following body systems will be examined: General Appearance, Skin, HEENT, Heart, Lungs, Musculoskeletal System, Lymph Nodes, Neurological Systems, Gastrointestinal System, Genitourinary System, Extremities and Other if necessary. Each body system will be classified as Normal, Abnormal Not Clinically Significant or Abnormal Clinically Significant.

Number and percentage of subjects with each assessment result will be tabulated by body system, visit and treatment group. All results will be listed.

7.8.5 Visual Acuity

Subjects' visual acuity will be measured during Visit 1 Screening, Visit 4 Day 7 +/-2and Visit 5 Day 14+/-2. Visual acuity will be tested using the subjects best-available spectacle correction with a Snellen chart. Best Corrected Visual Acuity will be recorded in Snellen units.

Snellen denominator and its change from baseline will be summarized descriptively by eye (study or non-study) visit and treatment group.

All results will be listed.

7.8.6 Slit Lamp Examination

Complete slit-lamp evaluation including evaluation of eyelids, conjunctiva, sclera, cornea and iris will be performed at Visit 1 Screening, Visit 3 Day 1, Visit 4 Day 7+/-2 and Visit 5 Day 14+/-2. Each eye area examined will be classified as Normal, Abnormal Not Clinically Significant or Abnormal Clinically Significant.

Number and percentage of subjects with each assessment result will be tabulated by eye (study or non-study), eye area, visit and treatment group. All results will be listed.

7.8.7 Intraocular Pressure

Intraocular pressure will be measured in mmHg at Visit 1 Screening, Visit 3 Day 1, Visit 4 Day 7+/-2 and Visit 5 Day 14+/-2.

Intraocular pressure and its change from baseline will be summarized descriptively by eye (study or non-study) visit and treatment group.

All results will be listed.

7.8.8 Dilated Fundus Examination

A dilated fundus examination will be administered at Visit 1 Screening and Visit 5 Day 14+/-2. In it, appropriate eye drops will be used to dilate or enlarge the pupil in order to obtain better view of the fundus of the eye. Once the pupil is dilated, an ophthalmoscope or indirect lens will be used to view the eye structures:

1. Optic Nerve Head: classified as Normal or Glaucomatous; horizontal and vertical cup/disc ratio measured.
2. Lens: examined for opacities and other challenges; classified as Normal, Abnormal Not Clinically Significant or Abnormal Clinically Significant
3. Vitreous: classified as Normal, Abnormal Not Clinically Significant or Abnormal Clinically Significant
4. Retina: classified as Normal, Abnormal Not Clinically Significant or Abnormal Clinically Significant

Number and percentage of subjects with each kind of assessment will be tabulated by eye (study or non-study), fundus structure, visit and treatment group. Horizontal and vertical cup/disc ratios will be summarized descriptively by eye (study or non-study), visit and treatment group.

7.8.9 Exposure to Product

The subjects will be instructed to use the diary to document all doses taken. Additionally, the dose taken one day prior to the surgery will be recorded on the eCRF.

Compliance with scheduled application of IP will be determined from the subject's diary as [Actual number of doses] / [Planned number of doses] * 100%, where

- Actual number of doses will counted from the subject diary and relevant eCRF pages;
- Planned number of doses is 17 (i.e. Days -1 through Day 14 with two doses taken on Day 0).

Number of missed doses will be calculated as the number of planned dosing time-points when the study drug was not taken during the 16 days starting with the date of the first dose. There is one dosing time-point per each day, except the day of Visit 2 Day 0, when there are two planned time-points, before the surgery and after the surgery.

Subjects who missed dosing for more than 3 consecutive days will be considered non-compliant and will be excluded from the PP population.

Subjects can be additionally excluded from the PP population due to non-compliance, if the Investigator's and Sponsor's review of their dosing times suggests a clinically meaningful departure from the once-daily dosing pattern.

Subjects will be considered compliant if they administer at least 14 doses and not more than 20 doses, with no more than 3 consecutive missed dosing days. The compliance will be analyzed using the descriptive statistics by treatment group. The proportion of compliant vs. non-compliant subjects will be tabulated for each treatment.

Duration of exposure will be calculated as Date of last use of the study drug – Date of first use of the study drug + 1. Duration of exposure will be summarized descriptively by treatment group.

Compliance, number of doses and duration of exposure will be summarized for the Safety and mITT populations.

7.8.10 Exposure to Concomitant Medication

Medication or non-drug therapy will be classified as prior, if the end date is known and is prior to the first use of the study drug. Medications and non-drug therapies that are ongoing or ended after the first use of the study drug will be classified as concomitant. If the end date of the medication or non-drug therapy is unknown, it will also be considered concomitant.

The concomitant medications will be summarized by preferred term for each treatment group as coded by the World Health Organization Drug (WHODRUG) dictionary Sept-2017 and be listed in a by-subject listing. Prior medications will be listed only.

7.8.11 Other assessments

Details of contraception method used by the subjects will be listed.

Urine pregnancy test will be performed for females of childbearing potential at Visit 1 Screening, Visit 2 Day 0 and Visit 5 Day 14. Results will be listed.

Details of the study drug and diary accountability will be listed.

General comments collected on the eCRF will be listed.

8. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

There are no changes from the protocol-specified analyses.

9. LIST OF PLANNED TABLES, FIGURES, AND LISTINGS

See separate document with the table, figure and listing shells.

10. LITERATURE CITATIONS / REFERENCES

1. Study Protocol: "A randomized, multicenter, double masked, placebo controlled, parallel group, bioequivalence study to evaluate the clinical equivalence and safety of Nepafenac 0.3% ophthalmic suspension ([redacted] Actavis LLC) with Ilevro™ (Nepafenac ophthalmic suspension), 0.3% of Alcon Laboratories, Inc. for the treatment of pain and inflammation associated with cataract surgery", version 2.0 dated Feb 22, 2018.

11. APPENDICES

11.1 Study visit Schedule

Visit Details	**Visit 1**	**Telephone Call**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Study Activities	**Day -7 to -1 Screening/ Baseline/ Randomization**	**Day -1 Pre-Operative Telephone Call**	**Day 0 The Day of Cataract Surgery**	**Day 1 One Day After Cataract Surgery**	**Day 7 ± 2 days Follow-up visit**	**Day 14 ± 2 days (End of Study / Early Discontinuation)**
Informed Consent Process	×					
Medical History & Demographics	×					
Pre-Operative Call		×				
Physical Examination	×					×
Vital Signs	×		×	×	×	×
Inclusion/Exclusion Review	×					
Schedule the day for Cataract Surgery	×					
Assessment of Ocular Pain	×			×	×	×
Visual Acuity	×				×	×
Slit Lamp Examination	×			×	×	×
Intraocular Pressure	×			×	×	×
Fundus Examination	×					×

Laboratory Assessments (hematology, biochemistry and urine analysis)	×					×
Urine Pregnancy Test	×		×			×
Dispense/Administer Study drug	×		×	×	×	×
Dispense Subject Diary	×			×	×	
Retrieval/Review of Subject Diary					×	×
Retrieval of Study Medication						×
Concomitant Medication Assessment	×		×	×	×	×
Adverse Event Assessment	×	×	×	×	×	×

11.2 Aqueous Cells Scale

Grade	**Aqueous Cells:** Determined using a narrow slit beam (0.5 mm width at least 8mm length) at maximum luminance. Pigment and red blood cells are to be
0	None
1	1 to 5 cells
2	6 to 15 cells
3	16 to 30 cells
4	Greater than 30 cells

11.3 Aqueous Flare Scale

Grade	**Aqueous Flare:** Determined using a narrow slit beam (0.5 mm width at least 8mm length) at maximum luminance.
0	No visible flare when compared with the normal eye.

1	Mild-Flare visible against dark pupillary background but not visible against iris background.
2	Moderate-Flare is visible with the slit-lamp beam aimed onto the iris surface as well as the dark pupillary background.
3	Severe-Very dense flare. May also present as a "hazy" appearance of anterior segment structures when viewed with low power magnification of the slit-lamp. Present as pronounced Tyndall effect.

11.4 Ocular Pain Scale

Grade	**Ocular Pain:** A positive sensation of the eye, including foreign body sensation, stabbing, throbbing or aching.
0	None- absence of positive sensation
1	Patient reports presence of mild sensation or discomfort typical of post-operative ocular surgery, e.g., diffuse or focal foreign body sensation, mild transient burning or stinging.
2	Mild- mild, tolerable aching of the eye.
3	Moderate- moderate or more prolonged aching sufficient to require the use of over-the-counter analgesics (e.g. acetaminophen).
4	Moderately Severe- More prolonged aching requiring the use of any over-the-counter analgesics other than acetaminophen.
5	Severe- Patient reports intense ocular, periocular, or radiating pain (e.g., constant or nearly constant sharp stabbing pain, throbbing or aching, etc.) requiring prescription analgesics.

11.5 Code Fragments

Superiority analysis

```
proc freq data=<dataset>
   tables <treatment>*<cure> / fisher;
run;
```

Note: this analysis needs to be performed separately for test and reference treatments on a dataset containing only test and placebo or reference and placebo treatment subjects.

Clinical equivalence analysis

```
proc freq data=<dataset>
    tables <treatment>*<cure > / riskdiffc;
run;
```

Note: this analysis needs to be performed on a dataset containing test and reference treatment subjects only.