U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA202872
Supplement #:	SUPPL-1
Drug Name:	Lotemax (loteprednol etabonate ophthalmic gel, 5%)
Indication(s):	Treatment of postoperative inflammation following ocular surgery for childhood cataract
Applicant:	Bausch & Lomb Inc.
Date(s):	Stamp Date: October 11, 2017 PDUFA Date: August 11, 2018
Review Priority:	Standard Review
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Keywords: **A**nterior Chamber Inflammation, Childhood Cataract

Table of Contents

LIST OF TABLES

1 EXECUTIVE SUMMARY

Bausch & Lomb Inc. (the Applicant), submitted this NDA supplement in response to the FDA's post-marketing pediatric data requirement for Lotemax (Loteprednol Etabonate Ophthalmic Gel, 0.5%). Lotemax was approved in 2012 by the FDA for the treatment of postoperative inflammation and pain following ocular surgery *in adults*. The main purpose of this review is to evaluate whether Lotemax is safe and effective for the treatment of postoperative inflammation following ocular surgery *for childhood cataract*. Additionally, this review will recommend text and efficacy summary for the drug labeling.

The Applicant conducted a Phase 4, multicenter, randomized, double-masked, parallel-group, active-controlled, non-inferiority pediatric study (Study 670). The primary objective of Study 670 was to compare the efficacy and safety of Lotemax to Prednisolone (Prednisolone Acetate Ophthalmic Suspension, 1%). In this study, 107 subjects between the ages of 0 to 11 years were randomized in a 1:1 ratio to receive either Lotemax (N=54) or Prednisolone (N=53) in the designated study eye. The total duration of the study was 90 days. Efficacy and safety assessments were conducted at post-operative Days 1, 7, 14, 28, 42 and 90. In both arms, subjects were eligible for rescue therapy if a) the study eye had a greater than anticipated inflammation at Day 1, or b) at the following visits, the inflammation in the study eye has worsened or did not show improvement compared to a previous visit. Subjects requiring rescue therapy were to stop treatment with study medication and to be exited from the study.

For each subject, anterior chamber inflammation (ACI), the primary efficacy outcome, was graded on a 5-unit scale [0 (None), 1 (Mild), 2 (Moderate), 3 (Severe) and 4 (Very Severe)]. The primary efficacy endpoint was the mean grade of ACI at postoperative Day 14. The primary efficacy analysis evaluated the non-inferiority of Lotemax against Prednisolone with respect to the primary efficacy endpoint on the ITT population. Missing ACI data, and ACI data for subjects who received rescue therapy prior to the evaluation of the primary efficacy endpoint was imputed using the last observation carried forward (LOCF) approach. The non-inferiority of Lotemax would be established if the upper limit of the 95% confidence interval for the treatment difference (Lotemax minus Prednisolone) is less than the pre-specified non-inferiority margin of 0.35.

The study demonstrated the non-inferiority of Lotemax to Prednisolone for the treatment of postoperative inflammation following ocular surgery for childhood cataract. The mean difference in ACI grade at postoperative Day 14 was 0.006 (95% CI: -0.281, 0.292). A higher proportion of Lotemax treated subjects (22.2%) received rescue therapy compared to subjects treated with Prednisolone (7.5%; Table 1). Note, at postoperative Day 14, 30 (57%) subjects randomized to Lotemax and 33 (63%) subjects randomized to Prednisolone achieved complete clearing of the ACI without requiring rescue therapy (difference: -7% (95% CI: -26%, 12%); Table 2).

Regarding safety, 23 (42.6%) subjects treated with Lotemax and 26 (49.1%) treated with Prednisolone reported at least one adverse event. The most common adverse events reported for Lotemax were eye pain (9.3%), eyelid oedema (7.4%), and ocular hyperemia (5.6%). None of

the Prednisolone treated subjects, and two of the Lotemax treated subjects reported serious adverse events. One subject in each treatment arm withdrew from the study due to an ocular adverse event in the study eye. No deaths were reported in either arm in this study.

In conclusion, the findings from the analyses presented in this statistical review provide evidence that Lotemax is effective for the treatment of postoperative inflammation following ocular surgery for childhood cataract.

Table 1: Summary of Primary Efficacy and Rescue Therapy Use

Visit	Mean (SE) ACI Grade (ITT)[1]		
	Treatment		Difference (95% CI)
	Lotemax N = 53	Prednisolone N=52	
Day 1	1.273 (0.12)	1.371 (0.12)	-0.099 (-0.34, 0.14)
Day 7	0.904 (0.13)	0.803 (0.13)	0.101 (-0.16, 0.36)
Day 14	**0.644 (0.14)**	**0.638 (0.14)**	**0.006 (-0.28, 0.29)**
Day 28	0.253 (0.12)	0.339 (0.13)	-0.086 (-0.34, 0.17)
Day 42	0.187 (0.12)	0.188 (0.12)	-0.001 (-0.25, 0.24)
Day 90	0.167 (0.12)	0.191 (0.12)	-0.024 (-0.27, 0.22)
Rescue Use on or Prior to a given Visit (Safety)[2]			
Visit	**Lotemax N=54**	**Prednisolone N=53**	**Difference (95% CI)**
Day 7	10 (18.5%)	2 (3.8%)	14.7% (3.2%, 26.3%)
Day 14	11 (20.4%)	3 (5.7%)	14.7% (2.3%, 27.1%)
Day 28	12 (22.2%)	4 (7.5%)	14.7% (1.5%, 27.8%)

Source: [1] Table 11-1 of the study reports Missing ACI data due to all reasons including data after subjects received rescue therapy is imputed using a prior non-missing ACI outcome (LOCF) The efficacy summary results for Day 1, 7, 28 and 42 are produced by the reviewer ITT (intent to treat): All randomized subjects who have at least one post-treatment assessment Subjects are analyzed under the treatment to which they were randomized (ITT-principle) Two subjects (one from each arm) who received at least one dose of study drug did not have post-surgery data and hence were excluded from the ITT population [2] Source: Adapted from Table 14 1 5 3 of the study report The distribution of rescue use over time and the 95% CI for the treatment differences is calculated by the reviewer Safety: Safety analysis set which includes subjects who received at least one dose of the study drug Subjects are analyzed under the treatment they received

Table 2: Proportion of Subjects with Clearing of Anterior Chamber Inflammation by Visit

Visit	Proportion of Subjects with Clearing of Anterior Chamber Inflammation (Grade Zero) without Rescue Therapy (ITT)		
	Treatment		Difference (95% CI)
	Lotemax N =53	Prednisolone N=52	
Day 1	30 (57%)	24 (46%)	10% (-9%, 29%)
Day 7	24 (45%)	29 (55%)	-10% (-30%, 9%)
Day 14	30 (57%)	33 (63%)	-7% (-26%, 12%)
Day 28	39 (74%)	39 (75%)	-1% (-18%, 15%)
Day 42	39 (74%)	43 (83%)	-9% (-25%, 7%)
Day 90	40 (75%)	43 (83%)	-7% (-23%, 8%)

Source: Reviewer's Analysis Subjects who received recue therapy prior to efficacy evaluation were set as treatment failures (ACI grade >0) Missing ACI data due to reasons other than rescue use is imputed using a prior non-missing ACI outcome (LOCF)

Labeling Recommendations (See Section 5.3 for Details)

The applicant proposed the following text for the Pediatric Use (8.4) sections of the label.

(b) (4)

However, to be consistent with previous NDA labeling, and to provide easily interpretable results for prescribing physicians, the statistical review team proposes the following text for Section 14 of the drug labeling.

The safety and effectiveness of LOTEMAX was evaluated in a pediatric study of patients from birth to less than 11 years of age (mean age of 3 years) who were undergoing routine, uncomplicated surgery for childhood cataract. One-hundred seven patients were randomized to receive either LOTEMAX (N=54) or prednisolone acetate ophthalmic suspension 1% (N=53) four times daily for 14 days. At Day 14, the percentage of patients with complete clearing of anterior chamber inflammation was 57% in the LOTEMAX group and 63% in the prednisolone group, with a treatment difference of -7% (95% CI: -26%, 12%).

2 INTRODUCTION

This NDA supplement included safety and efficacy data from one Phase 4 study to support the safety and efficacy of Lotemax for the treatment of post-operative inflammation following surgery for childhood cataract.

2.1 Overview

This section provides a brief overview of the class and indication of the studied drug, the history of the drug development, and outlines the specific studies reviewed.

2.1.1 Drug Class and Indication

The Applicant states that Lotemax contains the active ingredient loteprednol etabonate. Per the applicant, loteprednol etabonate is a potent corticosteroid and an analogue of Prednisolone. Lotemax is approved for several indications including seasonal allergic conjunctivitis (SAC), giant papillary conjunctivitis (GPC), uveitis and postoperative inflammation. The specific formulation studied in this NDA supplement is loteprednol etabonate ophthalmic gel, 0.5%. This formulation is indicated for the treatment of post-operative inflammation and pain following ocular surgery in adults.

2.1.1 History of Drug Development

Lotemax (loteprednol etabonate ophthalmic gel) 0.5% was approved for the treatment of post-operative inflammation and pain following ocular surgery in adults in September 2012. The Phase 3 studies used to support the safety and efficacy of Lotemax in adults did not enroll pediatric patients. The NDA application however included a pediatric study plan (study protocol). Because the application was ready for approval in adults, the Agency granted the Applicant a deferral of the pediatric study until 12/31/2016 (which was later extended to June 30, 2017). In the approval letter dated 09/28/2012, the Agency requested the Applicant to conduct the deferred pediatric study (Study 670) as a post-marketing requirement (PMR). The protocol and the statistical analysis plan for this study were reviewed under IND102654.

The original protocol for Study 670 was submitted on 12/05/2011 under a special protocol assessment (SPA) and was later amended six times. In the original protocol, the primary efficacy analysis planned to test the non-inferiority of Lotemax against Prednisolone with respect to the mean grade of converted ACI at postoperative Day 29 on the per-protocol population. The non-inferiority of Lotemax was to be demonstrated if the upper limit of the one-sided upper 97.5% confidence interval about the difference between the means is less than 0.35. The Agency disagreed with the timing of the primary efficacy analysis and recommended that the primary efficacy analysis be conducted on Day 7/8 or Day 14/15 instead of the proposed Day 29.

Reviewer's Remarks: This reviewer was not able to locate a statistical review for the original protocol for Study 670.

In the first protocol amendment (05/26/2011), the primary efficacy endpoint was changed to mean ACI grade at Day 14 and the analysis method was changed from a one-sided 97.5% confidence interval to a two-sided 95% confidence interval. The analysis population was also changed from the per-protocol to the intent to treat (ITT) population.

The second protocol amendment (11/15/2011) reversed the study population to the per-protocol population for the primary efficacy analysis. The remaining changes were mainly clarifications.

Reviewer's Remark*: After the review of the amended protocol, the statistical reviewer had the following comments regarding the non-inferiority margin, the primary efficacy endpoint and the analysis population:*

- *The non-inferiority margin of 0.35 is too generous for the proposed endpoint at any time points (day 8, day 15 or day 18). We recommend either using a different endpoint or changing the margin.*

- *Although per protocol (PP) analysis may be used as a primary analysis for a noninferiority trial, we believe that intent to treat (ITT) analysis is also very important and any discrepancy between ITT analysis and PP analysis should be explained.*

No major changes were made in the third protocol amendment (12/15/2011). The 4th protocol amendment (03/27/2012) made several major changes. In this version of the protocol, the number of subjects was changed from 170 to 158. The primary efficacy endpoint was changed to the mean grade of ACI at Day 7 (was mean converted anterior chamber grades at Day 14). The non-inferiority of Lotemax was to be established if the upper limit of the 95% confidence interval for the treatment difference is less than 0.5 (the previous version used 0.35 as a non-inferiority margin). Per the Applicant, the non-inferiority margin of 0.5 was justified based on the results of the Phase 3 trials of Lotemax against placebo in the adult population. The primary efficacy analysis was to be conducted on the per-protocol population with observed data only. Data after rescue use and missing data for other reasons were to be excluded. The primary efficacy endpoint would also be analyzed on the ITT population with LOCF as supplemental analysis.

Reviewer's Remark*: After reviewing version 4 of the study protocol, the statistical reviewer agreed to the non-inferiority margin of 0.5 and provided the following comment regarding sensitivity analysis: "In order to examine the robustness of the primary analysis using LOCF, we recommend you conduct sensitivity analyses for missing values. References for methods handling missing values are provided in the National Academies of Science Report on Prevention and Treatment of Missing Values in Clinical Trials."*

The 5th protocol amendment (06/05/2012) elaborated on the LOCF approach and edited typographical errors. In addition, in response to the statistical reviewer's recommendation for sensitivity analysis, the Applicant proposed a pattern mixture model under the missing not at random (MNAR) assumption for missing data.

An agreement on the SPA was reached on 07/27/2012. Subsequently, the Agency sent a formal written request for pediatric Study 670 on 04/26/2013. The Applicant accepted the written request and agreed to conduct the study within the terms of the written request. The following were two of the suggested changes to the protocol in the written request:

- *Trial endpoints: The primary endpoint for the trial must be mean grade of anterior chamber inflammation at Postoperative Day 14. The scale used for anterior chamber inflammation should be a 0-4-point scale where a Grade of 0 must equal zero cells. The assessment of anterior chamber inflammation at Postoperative Day 14 is considered an efficacy and safety trial endpoint.*

- *Statistical: For the primary efficacy analysis, the mean grade of anterior chamber inflammation at Postoperative Day 14 must be calculated by treatment group, including a two-sided 95% Confidence Interval (CI) about the difference between the means. A sample size of 120 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% using a non-inferiority upper limit of 0.35. This sample size assumes a common standard deviation of 0.47 and an expected difference of 0 for the difference in means between treatment groups using anterior chamber inflammation at Visit 5 (Postoperative Day 14).*

The sixth and final amended protocol incorporated the items included in the written request. The non-inferiority margin was changed from 0.5 to 0.35 (as per-FDA written request). In addition, the timing of the primary efficacy analysis was changed from Day 7 to Day 14. Additional changes included the change of the study population for the primary efficacy analysis from per-protocol to ITT, change in the phase of the study from 3b to 4, change in the number of subjects to be enrolled from 158 (79 aged 0-3) to 140 (60 aged 03), the study duration from 12-18 weeks to 11-19 weeks. Changes were also made to the definition of the visit windows.

According to the Applicant, the statistical analysis plan dated 06/04/2012 was amended to version 2 dated 05/12/2017 to reflect the changes made based on amendment 6 of the study protocol. In addition to changes made to reflect the amended protocol, the SAP made some additional changes independent of the changes in the protocol. One of the major changes is the inclusion of investigational site as covariate in the primary efficacy analysis of the mean ACI grade. The other major change was the inclusion of the following description regarding how the ACI grade is calculated "*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.*"

Other notable changes include the deletion of a section describing an ANCOVA approach in which baseline ACI measurements were included as covariates in the analysis of the primary efficacy endpoint, and the omission of the proposed sensitivity analysis using the pattern mixture model.

2.1.2 Studies Reviewed

This NDA review was conducted based on data from Study 670. This study enrolled 107 subjects from a total of 11 sites (Table 15). The Applicant's summary for this study is presented in (Table 3).

Table 3: Summary of Study 670

Design	Treatment/Sample size	Endpoint/Analysis	Applicant's findings
A Phase 4, multicenter, randomized, double-masked, parallel-group, and active-controlled non-inferiority study. The primary objective of this study was to evaluate the efficacy of Lotemax for the treatment of postoperative inflammation following ocular surgery for childhood cataract.	– Lotemax (LE): N=54 – Prednisolone (PA): N=53	Primary Endpoints: Mean anterior chamber inflammation of the study eye at Day 14. The primary efficacy analysis of evaluating the non-inferiority of Lotemax against Prednisolone was conducted on the ITT population consisting of all randomized with at least one post-treatment assessment. The non-inferiority margin of 0.35 units was considered. For the analysis of the primary efficacy variable, missing data due to all reasons including using of a rescue therapy was imputed using the last observed value (LOCF).	The study met the primary endpoint [sic] of demonstrating non-inferiority of LE Gel to PA Suspension for the treatment of postoperative inflammation following ocular surgery for childhood cataract. At Visit 5 (Postoperative Day 14), the LS mean difference between treatment arms (LE Gel – PA Suspension) for mean grade of ACI in the study eye was 0.006 (95% CI: -0.281, 0.292) for the ITT population with LOCF. The upper 95% CI on the difference was < 0.35, the pre-specified criterion for non-inferiority (p=0.0094; one-sided test).

Source: Adapted from the Applicant's study reports LS: least squares

2.2 Data Sources

The data sources for this review included the Applicant's clinical study reports and SAS datasets electronically submitted both as SDTM and ADAM data formats. The datasets used in this review are located at: \\Cdsesub1\evsprod\NDA202872\0054\m5\datasets. The clinical study report is located at: \\Cdsesub1\evsprod\NDA202872\0051.

The efficacy outcomes collected at screening and subsequent measurement times are included in the *adbio.xpt* dataset. An indicator variable (PARAMCD) is included to distinguish between the different outcomes (inflammation, flare, cells). For the primary efficacy analysis of the inflammation outcome, the variable *AVAL* which takes values of 0,1,2,3 and 4 is provided. The treatment variable, given both as numeric (TRT01P) and character (TRT01PN), is also included in the *adbio.xpt* dataset. The data containing treatment exposure and adverse events is *adae.xpt*. An indicator variable for rescue use (RESCUEFL) and the date of rescue therapy (RESSDT) are given in the *adcm.xpt* dataset.

3 STATISTICAL EVALUATION

This section provides a detailed summary of the study design and results of Study 670.

3.1 Data and Analysis Quality

The quality of the datasets was sufficient for this review. The reviewer reproduced the Applicant's primary efficacy and safety results using the submitted datasets. The final statistical analysis plan and the amended protocols were all submitted.

3.2 Evaluation of Efficacy

This section summarizes the design of the study and the corresponding efficacy results.

3.2.1 Study Design and Endpoints

Study 670 was a multicenter, randomized, double-masked, parallel-group, active-controlled, non-inferiority pediatric study. This study enrolled 107 subjects between the ages of 0 and 11 years who were undergoing routine, uncomplicated surgery for childhood cataract. Exclusion criteria disallowed subjects who had severe/serious ocular condition, or any other unstable medical condition that, in the investigator's opinion, may preclude study treatment or follow-up. Additionally, subjects who had suspected permanent low vision or blindness and subjects who had ocular surgery (including laser therapy) in the study eye within 90 days prior to randomization were also excluded.

Subjects who met all inclusion and none of the exclusion criteria were randomized in a 1:1 ratio to receive either Lotemax or Prednisolone in the designated study eye. The dose regimen was the same for both treatment groups. One to two drops of study drug were instilled into the lower cul-de-sac of the study eye immediately following surgery, and on the evening of surgery. Thereafter, both treatments were dosed QID, at approximately 4-hour intervals, for the first 14 days. The treatments were then tapered to BID from postoperative days 15 through 21, and then further tapered to QD from postoperative Day 22 until the day prior to postoperative Day 28. Subjects underwent safety and efficacy examinations on post-operative days 1, 7, 14, 28, 42, and 90.

The primary efficacy outcome of ocular inflammation was assessed via Biomicroscopy performed by an ophthalmologist. Use of fixed or handheld slit lamp or ophthalmic operating microscope was preferred; however, use of a penlight with a 20D magnifying lens was permitted if slit lamp examination was not possible. For subjects where the slit lamp method was used, the ACI grade is derived as the maximum of the anterior chamber flare (ACF) and the anterior chamber cell (ACC) grades. The penlight, however, directly grades the ACI as shown in the table below. Please see the Appendix for further description of the ACC, ACF and ACI grades.

ACC Grade	ACF Grade	ACI Grade[1]	
		Slit Lamp	Penlight
0= None (No cells)	0=None	0=None (Grade 0 cells and flare)	Grade 0
1=1-5 Cells	1=Mild	1=Mild (Maximum of cells and flare grade is 1)	Grade 1
2= 6-15 Cells	2=Moderate	2= Moderate (Maximum of cells and	Grade 2

		flare grade is 2)	
3= 16-30 Cells	3=Severe	3=Severe (Maximum of cells and flare grade is 3)	Grade 3
4= >30 cells	4=Very Severe	4=Very Severe (Maximum of cells and flare grade is 4)	Grade 4

Reviewer's Remark*: From the data, it appears that, for 94 (89%) of the 105 subjects included in the ITT analysis, only the Slit lamp was used at all visits. However, for 10 subjects, the ACI grade was derived using the Penlight for some visits while other visits used the Slit lamp. For one subject, the ACI grades were derived using the Penlight at all visits. Subjects using either Slit lamp or Penlight method have ACI grades, but only those subjects using Slit lamp method have ACC and ACF grades. This means, 11 subjects would have ACI data but no ACC and ACF data for the time points where a Penlight only is used (See Appendix B Table 12).*

	Treatments (ITT)		
Method	*Lotemax N=53*	*Prednisolone N=52*	*Total N=105*
Slit lamp only at all visits	*50 (94,3%)*	*44 (84.6%)*	*94 (89.5%)*
Penlight only at all Visits	*1 (0.9%)*	*0 (0.0%)*	*1 (0.9%)*
Slit lamb and Penlight	*2 (1.8%)*	*8 (15.4%)*	*10 (9.5%)*

The primary efficacy endpoint was the mean grade of ACI at postoperative Day 14. The study had the following secondary efficacy endpoints:

- Mean grade of ACI at postoperative Days 7 and 28
- Proportion of subjects with ACI Grade 0, Grade 1, Grade 2, Grade 3, and Grade 4 at postoperative Days 7, 14, and 28
- Proportion of subjects with Presence/absence and total area, if present, of synechiae at postoperative Days 7, 14, and 28.
- Proportion of subjects with Presence/absence and total number, if present, of precipitates on the implant and cornea at postoperative Days 7, 14, and 28

Safety was monitored at each visit and included adverse events, measurements of intraocular pressure (IOP) and visual acuity, and assessment of ocular signs by biomicroscopic examinations. Subjects were also assessed at postoperative Days 1, 7, 14, and 28 to determine whether they needed rescue therapy. In both arms, a study eye with greater than anticipated inflammation at Day 1 or, at the following visits, a worsening or no change of the grade of inflammation compared to the previous visit was eligible for rescue therapy. Subjects requiring rescue therapy for inflammation were to stop treatment with study medication and to be exited from the study.

Reviewer's Remark*: The adult studies for Lotemax had two primary efficacy endpoints. The complete resolutions of Pain and the complete resolution of ACC (ACC grade =0) at Day 8. In both endpoints (Pain and ACC clearing), subjects who received rescue therapy were treated as treatment failures. ACC was measured using a slit beam and was graded using the same 5-unit scale used in this pediatric study. In the adult studies, subjects must have an ACC grade of 2 or more at post-operative Day 1 to be randomized. This was not the case for the pediatric study.*

3.2.2 Statistical Methods

3.2.2.1 Analysis Populations

The statistical analysis plan and the study protocol defined the following three major analysis sets for the evaluation of efficacy and safety:

- Intent-to-treat (ITT) analysis set: All randomized subjects who have at least one post-treatment assessment. Subjects are analyzed under the treatment to which they were randomized (ITT-principle).

- Per-protocol (PP) analysis set: All 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.

- Safety analysis set: Subjects who received at least one dose of the study drug. Subjects are analyzed under the treatment they received.

3.2.2.2 Analysis Methods

The primary efficacy analysis evaluated the non-inferiority of Lotemax against Prednisolone with respect to the mean grade of ACI at postoperative Day 14 on the ITT population. Data for subjects who received rescue therapy prior to the evaluation of the primary efficacy endpoint, and for subjects with missing ACI grade for other reasons were imputed using the LOCF approach.

The protocol-defined primary efficacy analysis used an ANOVA model with treatment and investigational site as covariates. The least squares mean for each treatment group, the difference in the least squares mean between the two treatment arms (Lotemax minus Prednisolone), and the 2-sided 95% confidence interval for the treatment difference were constructed. The non-inferiority of Lotemax against Prednisolone would be established if the upper limit of the confidence interval for the treatment difference is less than 0.35 (the non-inferiority margin).

The Applicant used the same ANOVA approach for the analysis of the primary efficacy endpoint on the ITT and PP populations with observed data only. The Applicant also used the same ANOVA approach for the analyses of continuous secondary efficacy endpoints. For binary secondary efficacy endpoints, the Applicant presented differences in proportions between treatment arms and an asymptotic 2-sided 95% confidence interval about the differences. The Applicant's analyses of the secondary efficacy endpoints were conducted on the ITT population and on the PP population with observed data only. The Applicant did not make any multiplicity adjustments.

The reviewer used a cumulative odds logistic regression model to compare the two treatment arms with respect to the odds of having a lower ACI grade (ACI grade $\leq$j, j=0,1,2,3,4) versus a higher ACI grade at Day 14. In this analysis, for each subject, the ACI grade (0, 1, 2, 3, and 4)

was used as a response variable and treatment was included as the only covariate. Only observed data was used. A brief description, and a sample SAS code for the cumulative logistic regression model is provided in the Appendix. The reviewer also conducted the analysis of the primary efficacy endpoint and continuous secondary efficacy endpoints using an ANOVA model with treatment as the only covariate. For binary secondary efficacy endpoints, the reviewer provided proportions and asymptotic 95% confidence intervals for treatment differences. These analyses were conducted on both the ITT and the PP populations. Missing data and data after rescue use were imputed using different approaches (LOCF, treating rescue use as failure and observed data only).

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

3.2.3.1 Subject Disposition

The subject disposition summary is presented in Table 4. As can be seen from the table, all randomized subjects were treated. However, one subject from each treatment arm received the treatment he/she was not randomized to. A total of 14 (25.9%) and 10 (18.9%) subjects randomized to the Lotemax and Prednisolone arms, respectively, discontinued the study. In both arms, the main reason for study discontinuation was the initiation of rescue therapy.

Table 4: Subject Disposition (Study 670)

Disposition	**Lotemax n (%)**	**Prednisolone n (%)**	**All Subjects n (%)**
Randomized	54	53	107
Treated as Randomized	53 (98.1%)	52 (98.1%)	105 (98.1%)
Treated Not as Randomized	1 (1.9%)	1 (1.9%)	2 (1.9%)
Included in the ITT Population[1]	53 (98.1%)	52 (98.1%)	105 (98.1%)
Included in the PP Population	40 (74.1%)	43 (81.1%)	83 (77.6%)
Discontinued from the Study	14 (25.9%)	10 (18.9%)	24 (22.4%)
Withdrew Consent	0 (0.0%)	1 (1.9%)	1 (0.9%)
Lost to Follow-up	1 (1.8%)	1 (1.9%)	2 (1.9%)
Adverse Event	1 (1.8%)	1 (1.9%)	2 (1.9%)
Rescue Therapy[2]	11 (20.4%)	5 (9.4%)	16 (14.9%)
Failure to Follow Required Study Procedures	0 (0.0%)	1 (1.9%)	1 (0.9%)
Other Reason	1 (1.8%)	1 (1.9%)	2 (1.9%)

Source: Adapted from Table 10 of the applicant's study reports [1] Two subjects (one subject from each arm) were excluded from the ITT population because they had no ACI measurements after surgery One subject from each arm received the opposite treatment [2]The one subject who was randomized to Prednisolone but wrongly received Lotemax has later received a rescue therapy In this table, this subject is counted in his/her randomized treatment group (Prednisolone)

Note, in this study, ACI data is considered missing if subjects received rescue therapy prior to the evaluation of efficacy, or if their ACI measurement is missing for other reasons (e.g. lost-to-follow up). The summary of subjects with observed and missing ACI measurements categorized by reason for missing data (rescue use or other) is presented in Table 5. At Day14, 14 (26%) subjects in the Lotemax arm had missing data compared to 6 (12%) subjects in the Prednisolone arm. Of these subjects, 10 (19%) in the Lotemax arm and 3 (6%) in the Prednisolone arm had missing data because they received rescue therapy on or prior to Day 14.

Table 5: Summary of Subjects by Data Type: (ITT)

Visit	Data Type	Treatments		All Subjects N=105
		Lotemax N=53	Prednisolone N=52	
Day 1	Observed	53(100%)	51(98%)	104(99%)
	Missing	0(0%)	1(2%)	1(1%)
	Missing (Rescued)	0(0%)	0(0%)	0(0%)
Day 7	Observed	53(100%)	48(92%)	101(96%)
	Missing	0(0%)	3(6%)	3(3%)
	Missing (Rescued)	0(0%)	1(2%)	1(1%)
Day 14	Observed	39(74%)	46(88%)	85(81%)
	Missing	4(8%)	3(6%)	7(7%)
	Missing (Rescued)	10(19%)	3(6%)	13(12%)
Day 30	Observed	39(74%)	44(85%)	83(79%)
	Missing	4(8%)	4(8%)	8(8%)
	Missing (Rescued)	10(19%)	4(8%)	14(13%)
Day 42	Observed	39(74%)	43(83%)	82(78%)
	Missing	3(6%)	4(8%)	7(7%)
	Missing (Rescued)	11(21%)	5(10%)	16(15%)
Day 90	Observed	39(74%)	43(83%)	82(78%)
	Missing	3(6%)	4(8%)	7(7%)
	Missing (Rescued)	11(21%)	5(10%)	16(15%)

[1]Source: Reviewer's Analysis Observed: ACI data collected Missing: ACI data is missing due to reasons other than rescue use Missing (Rescued): ACI data is missing because the subject received a rescue therapy on or prior to that visit Subjects are summarized under the treatment to which they were randomized (ITT-principle)

[1]***Reviewer's Remark****: Some subjects received rescue therapy at a given visit after their ACI data for that visit was collected. Hence, these subjects will have observed ACI data for that visit but their subsequent data will be missing. Consequently, the number of subjects with missing data due to rescue use at a given visit and the number of subjects who received a rescue therapy on or prior to a given visit might be slightly different.*

3.2.3.2 Demographic and Baseline Characteristics

The demographic and baseline characteristics summary is presented in Table 6. As can be seen, the Lotemax arm had slightly more male subjects than female subjects. On the other hand, equal number of male and female subjects were enrolled into the Prednisolone arm. In both arms, study subjects were predominantly white, and had brown eyes.

Subjects' age ranged between 0 and 11 years with an average age of around 3.7 and 4.3 years in the Lotemax and Prednisolone arms, respectively. A total of 28 (52.8%) subjects in the Lotemax arm and 24 (46.2%) subjects in the Prednisolone arm were ≤ 3 years of age.

Table 6: Baseline and Demographic Characteristics (ITT)

	Treatments		All Subjects N=105
	Lotemax N=53	Prednisolone N=52	
Sex			
Male	31(58.5%)	26 (50%)	57 (53.3%)
Female	22 (41.5%)	26 (50%)	48 (44.8%)
Age (Years)			
Mean (SD)	3.7 (3.22)	4.3 (3.39)	4.0 (3.30)
Median	3.0	4.0	4.0
Min, Max	0, 11	0, 10	0, 11
Age Group			
≤3 Years	28 (52.8%)	24 (46.2%)	52 (49.5%)
>3 Years	25 (47.2%)	28 (53.8%)	53 (50.5%)
Race			
White	26 (49.1%)	23 (44.2%)	49 (46.7%)
Black or African American	8 (15.1%)	10 (19.2%)	18 (17.1%)
Asian	1 (1.9%)	1 (1.9%)	2 (1.9%)
Other	18 (34%)	18 (34.6%)	36 (34.3%)
Ethnicity			
Hispanic or Latino	24 (45.3%)	20 (38.5%)	44 (41.9%)
Not Hispanic or Latino	29 (54.7%)	32 (61.5%)	61 (58.1%)
Iris Color			
Blue	10 (18.9%)	8 (15.4%)	18 (17.1%)
Brown	38 (71.7%)	39 (75.0%)	77 (73.3%)
Green	1 (1.9%)	1 (1.9%)	2 (1.9%)
Hazel	3 (5.7%)	4 (7.7%)	7 (6.7%)
Other	1 (1.9%)	0 (0.0%)	1 (0.95%)

Source: Table 14.1.3.1 of the applicant's study reports

3.2.4 Results and Conclusions

3.2.4.1 Efficacy Results

3.2.4.1.1 *Primary Efficacy Analysis*

Study 670 demonstrated the non-inferiority of Lotemax to Prednisolone for the treatment of postoperative inflammation following ocular surgery for childhood cataract. The mean difference in ACI grade at post-operative Day 14 was 0.006 (95% CI: -0.281, 0.292; Table 7). However, a numerically higher proportion of subjects treated with Lotemax (22.2%) received rescue therapy compared to subjects treated with Prednisolone (7.5%; Table 7). Note, in both treatments arms, Prednisolone/prednisolone acetate was the rescue therapy used in all subjects except one subject in the Prednisolone arm who also received Atropine.

Table 7: Summary of Efficacy and Rescue Therapy Use

Visit	Mean (SE) ACI Grade (ITT)[1]		
	Treatment		Difference (95% CI)
	Lotemax N = 53	Prednisolone N=52	
Day 1	1.273 (0.12)	1.371 (0.12)	-0.099 (-0.34, 0.14)
Day 7	0.904 (0.13)	0.803 (0.13)	0.101 (-0.16, 0.36)
Day 14	**0.644 (0.14)**	**0.638 (0.14)**	**0.006 (-0.28, 0.29)**
Day 28	0.253 (0.12)	0.339 (0.13)	-0.086 (-0.34, 0.17)

Day 42	0.187 (0.12)	0.188 (0.12)	-0.001 (-0.25, 0.24)
Day 90	0.167 (0.12)	0.191 (0.12)	-0.024 (-0.27, 0.22)
Rescue Use on or Prior to a given Visit (Safety)[2]			
Visit	**Lotemax N=54**	**Prednisolone N=53**	**Difference (95% CI)**
Day 7	10 (18.5%)	2 (3.8%)	14.7% (3.2%, 26.3%)
Day 14	11 (20.4%)	3 (5.7%)	14.7% (2.3%, 27.1%)
Day 28	12 (22.2%)	4 (7.5%)	14.7% (1.5%, 27.8%)

Source: [1] Table 11-1 of the study reports Missing ACI data due to all reasons including data after subjects received rescue therapy is imputed using a prior non-missing ACI outcome (LOCF) The efficacy summary results for Day 1, 7, 28 and 42 are produced by the reviewer ITT (intent to treat): All randomized subjects who have at least one post-treatment assessment Subjects are analyzed under the treatment to which they were randomized (ITT-principle) Two subjects (one from each arm) who received at least one dose of study drug did not have post-surgery data and hence were excluded from the ITT population [2] Source: Adapted from Table 14 1 5 3 of the study report The distribution of rescue use over time and the 95% CI for the treatment differences is calculated by the reviewer Safety: Safety analysis set which includes subjects who received at least one dose of the study drug Subjects are analyzed under the treatment they received

Reviewer's Remark: *Although the ACI is graded in a 5-point scale (0-4), the most common grades given by investigators are 0-2. Grade 3 was rarely given and grade 4 was never given in Study 670.*

3.2.4.1.2 *Supplemental Analysis of the Primary Efficacy Endpoint*

The analysis of the primary efficacy endpoint conducted on the ITT and the PP populations with observed data only are supportive of the primary efficacy analysis results (Table 8). Note that, one Lotemax randomized subject wrongly received Prednisolone and one Prednisolone randomized subject received Lotemax. The subject who was randomized to Prednisolone but used Lotemax, ended up receiving a rescue therapy on Day 7. As per the study protocol, these two subjects were included in the primary efficacy analysis under the treatment they were randomized (*ITT-Principle*). The FDA's guidance for non-inferiority studies states that, unlike the superiority studies, the analysis following the ITT-principle might be less conservative for non-inferiority studies. The reviewer conducted the analysis of the primary efficacy endpoint with these subjects included under the treatment they received rather than randomized (*as-treated*). This analysis provided the same result as the as-randomized analysis (Table 8).

Table 8: Summary of Mean ACI Under Different Assumptions

Approach	**Treatment**		**Difference (95% CI)**
	Lotemax Mean (SE)	**Prednisolone Mean (SE)**	
ITT-Observed[1]	0.573 (0.11)	0.639 (0.11)	-0.066 (-0.3, 0.17)
PP- Observed[2]	0.57 (0.11)	0.613 (0.11)	-0.043 (0.29, 0.2)
ITT-LOCF (as-treated)[3]	0.644 (0.14)	0.638 (0.14)	0.006 (-0.28, 0.29)

[1] Source: Adapted from Table 14 2 1 3 of the study reports Only subjects in the ITT population who had ACI data at Day 14 are included in this analysis (Lotemax (N=39) and Prednisolone (N=46))

[2] Source: Table 11-1 of the study reports Only subjects with no protocol violations and have ACI data at Day 14 were included in this analysis (Lotemax (N=38) and Prednisolone (N=31))

[3] Source: Reviewer's Analysis Missing ACI data due to all reasons including data after subjects received a rescue therapy is imputed using a prior non-missing ACI outcome (LOCF) The two subjects who received the wrong treatments are analyzed according to the treatment they received (as-treated)

3.2.4.1.3 *Secondary Efficacy Endpoints*

The summary results for the analyses of secondary efficacy endpoints are presented in Figure 3-Figure 28 in the Appendix. Compared to the Prednisolone arm, the Lotemax arm had slightly higher mean ACI grades at Days 7 and 14. The mean ACI grades for Lotemax were however

slightly lower at Days 1, 28, 42 and 90 (Figure 3). The distribution of ACI grades (none, mild, moderate or severe) are presented in Figure 1 and Figure 2. The Prednisolone arm had slightly more subjects with ACI grades of "severe" for most of the study visits. The reviewer's cumulative logistic regression analysis shows that there was no difference between the two treatment arms with respect to the odds of having a lower inflammation category versus a higher category at Day 14 [Odds Ratio (95% CI): 1.008 (0.409, 2.484)].

In both arms, the proportion of subjects with ACI grade of zero (no inflammation) increased with time after Day 7. Subjects in the Lotemax arm had slightly lower rate of ACI grade of zero compared to the Prednisolone arm (Figure 6-Figure 9). At postoperative Day 14, 60% and 65% of subjects randomized to Lotemax and Prednisolone arms, respectively, achieved clearing of anterior chamber inflammation (ACI grade of zero) (Figure 6).

The reviewer provided summary results for the proportion of subjects with clearing of ACI without using rescue therapy (Figure 8). In this analysis, subjects who received rescue therapy on or prior to the evaluation of efficacy were set as treatment failures (ACI grade>0). The LOCF was used for missing data due to other reasons. At postoperative Day 14, 30 (57%) Lotemax randomized subjects achieved clearing of ACI (grade of zero) without using rescue therapy compared to 33 (63%) subjects in the Prednisolone arm.

Of the total of 16 subjects who received rescue therapy, the protocol defined rescue criteria was not met for 3 subjects (2 in the Lotemax arm and 1 in the Prednisolone arm). These three subjects had zero ACC, ACF and ACI grades at all visits prior to receiving the rescue therapy. Consequently, the results of the ACI analysis with LOCF for all missing data (including rescue use; Figure 6), and the analysis in which subjects who received rescue therapy treated as treatment failures while the LOCF used for missing ACI data due to other reasons (Figure 8), were slightly different. Please see the efficacy outcomes for subjects who received rescue therapy in Appendix B Table 14.

In both arms, there were very few subjects with Precipitates and Synechiae over the 90 days period. The proportion of subjects with absence of Precipitates and Synechiae was comparable between the two arms. At post-operative day 14, the proportion of subjects with no Precipitates was 92% in the Lotemax arm compared to 94% in the Prednisolone arm. The corresponding figures for the proportion of subjects with absence of Synechiae at Day 14 was 98% in both arms (Figure 24 and Figure 27).

Anterior Chamber Cell and Anterior Chamber Flare

Note that, except for subgroup analyses, neither the protocol nor the statistical analysis plan listed ACC and ACF grades as secondary efficacy endpoints. However, the applicant provided summary results for the mean ACC and ACF grades as well as the proportion of subjects with ACC and ACF grades of 0, 1,2, 3 and 4 in the study report.

The summaries of mean ACC and ACF grades and the proportion of subjects with clearing of the ACC and clearing of the ACF are presented in Figure 10-Figure 23. The Lotemax arm had consistently lower mean ACC grades for all study visits compared to Prednisolone. At Day 14,

the difference in mean ACC grade (Lotemax - Prednisolone) was -0.114 (95% CI: -0.41, 0.18; Figure 10). The mean difference in ACF at Day 14 was 0.031 (95% CI: -0.11, 0.18; Figure 17).

The proportion of subjects with clearing of the ACC ranged from 57% at Day 1 to 85% at Day 90 in the Lotemax arm compared to 50% and 88%, respectively, in the Prednisolone arm (Figure **13**). At postoperative Day 14, there was a 1% difference (68% vs 67%; Figure 13) in favor of Lotemax for the clearing of ACC. The treatment difference in the proportion of subjects with clearing of ACF at Day 14 was -3% (70% vs 73%; Lotemax vs. Prednisolone; Figure 20).

Reviewer's Remark*: Like the primary efficacy analysis, the as-treated analyses on the ITT population with LOCF provides the same result as the as-randomized analyses. The analysis on the ITT population with observed data were also only slightly different from the analysis based on the ITT-principle. The overall conclusion remains unchanged. Besides, because both subjects were excluded from the PP population, the as-treated and the as-randomized analysis results were the same for the analysis on PP population with observed data only.*

3.3 Evaluation of Safety

This section summarizes the safety findings from Study 670. The safety population was comprised of 54 subjects who received at least one dose of Lotemax and 53 subjects who received at least one dose of Prednisolone. A total of 23 (42.6%) subjects treated with Lotemax and 26 (49.1%) treated with Prednisolone reported at least one adverse event. The most common adverse events for Lotemax were eye pain (9.3%), eyelid oedema (7.4%), and ocular hyperemia (5.6%). Two subjects (3.7%) treated with Lotemax reported serious adverse events (Glaucoma and Bronchiolitis). No subject treated with Prednisolone reported a serious adverse event. One subject in each treatment arm withdrew from the study due to an ocular adverse event in the study eye, and no deaths were reported in either arm.

Table 9: Summary of Adverse Events (Safety Analysis Set)

	Treatments		
Adverse Event	**Lotemax N=54**	**Prednisolone N=53**	**All subjects N=107**
At least one AE (Ocular and non-ocular)	23 (42.6%)	26 (49.1%)	49 (45.8%)
At least one Serious AE	2(3.7%)	0 (0.0%)	2 (1.9%)
At least one ocular AE in the Study eye	13 (24.1%)	7 (13.2%)	20 (18.7%)
Amblyopia	1 (1.9%)	0 (0.0%)	1 (0.93%)
Conjunctivitis	0 (0.0%)	1 (1.9%)	1 (0.93%)
Conjunctivitis Viral	1 (1.9%)	0 (0.0%)	1 (0.93%)
Eye Discharge	1 (1.9%)	1 (1.9%)	2 (1.9%)
Eye Irritation	1 (1.9%)	0 (0.0%)	1 (0.93%)
Eye Pain	5 (9.3%)	2 (3.8%)	7 (6.5%)
Eyelid Oedema	4 (7.4%)	2 (3.8%)	6 (5.6%)
Glaucoma	1 (1.9%)	0 (0.0%)	1 (0.93%)
Iridocyclitis	0 (0.0%)	1 (1.9%)	1 (0.93%)
Lacrimation Increased	1 (1.9%)	0 (0.0%)	1 (0.93%)
Ocular Hyperaemia	3 (5.6%)	0 (0.0%)	3 (2.8%)
Photophobia	1 (1.9%)	0 (0.0%)	1 (0.93%)
Posterior Capsule Opacification	1 (1.9%)	0 (0.0%)	1 (0.93%)
Strabismus	1 (1.9%)	0 (0.0%)	1 (0.93%)
Vitreous Disorder	1 (1.9%)	0 (0.0%)	1 (0.93%)

Source Tables 12-2, 12-3, 12-4 of the study report. Some subjects have multiple AEs and hence were counted multiple times.

Visual acuity (VA) and intraocular pressure (IOP) were assessed in the study eye at screening, surgery day, and postoperatively Days 1, 7, 14, 28, 42 and 90. As can be seen in Table 10, the proportion of subjects with a ≥ 2-line worsening in VA from baseline was lower in the Lotemax arm compared to the Prednisolone arm at postoperative Days 1, 7 and 14.

Table 10: Proportion of Subjects with ≥2 Line Worsening in VA from Baseline (ITT-Observed)

Visit	Lotemax	Prednisolone	Difference (95% CI)
Day 1	4/22(18.2%)	8/25(32%)	-13.8% (-38.2%,10.6%)
Day 7	5/22(22.7%)	6/25(24%)	-1.3% (-25.5%,23%)
Day 14	1/13(7.7%)	2/21(9.5%)	-1.8% (-21%,17.3%)
Day 28	0/12(0%)	0/20(0%)	0% (0%, 0%)
Day 42	1/13(7.7%)	1/20(5%)	2.7% (-14.7%,20%)
Day 90	0/13(0%)	0/20(0%)	0% (0%, 0%)

Source: Adapted from Table 14.3.2.2 of the study reports. Only observed data was used. The 95% CI for the treatment differences is calculated by the reviewer. Subjects are summarized according to the treatment they received (as-treated).

At the surgery day, the mean IOP in the study eye was comparable between the two treatment arms (14.5mm Hg in the Lotemax arm and 14.7 mm Hg in the Prednisolone arm). The mean IOP in the study eye declined at all postoperative visits for both arms; with reductions in mean IOP ranging from 1.1 to 3.3 mmHg in the Lotemax arm, and from 1.2 to 4.0 mmHg in the Prednisolone arm (Table 11).

Table 11: Mean IOP Change from Baseline (ITT-Observed)

Visit	Lotemax Mean (SE)	Prednisolone Mean (SE)	Difference (95% CI)
Day 1	-3.3 (0.87)	-4.0 (0.89)	0.714(-1.77,3.2)
Day 7	-2.5(0.71)	-2.4 (0.76)	-0.106(-2.18,1.97)
Day 14	-2.9 (0.80)	-1.2 (0.72)	-1.7(-3.86,0.46)
Day 28	-2.3 (0.89)	-1.3 (0.80)	-1.065 (-3.45,1.32)
Day 42	-1.4 (0.83)	-2.9 (0.72)	1.549(-0.65,3.75)
Day 90	-1.1 (0.85)	-2.5 (0.78)	1.439(-0.86,3.74)

Source: Adapted from Table 14.3.5 of the study reports. Only observed data was used. The 95% CI for the treatment differences is calculated by the reviewer. Subjects are summarized according to the treatment they received (as-treated).

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The subgroup analyses results are presented in Figures 30-35. These results are considered descriptive and should only be used to characterize the observed treatment differences between subgroups. Overall, the subgroup analyses results showed that there was no noticeable difference in efficacy between the two arms across the different subgroups.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No major statistical issues were identified in this review.

5.2 Collective Evidence

This review evaluates the efficacy of Lotemax in one Phase 4 study, namely, Study 670. The efficacy results from Study 670 demonstrate that Lotemax is non-inferior to Prednisolone with respect to the mean ACI grade at Day 14 in the ITT population. A numerically higher proportion of subjects treated with Lotemax received rescue therapy compared to subjects treated with Prednisolone. Evaluations of efficacy using different secondary efficacy endpoints also support the results of the primary efficacy analysis.

5.3 Conclusions and Labeling Recommendations

The findings from the analyses presented in this statistical review provide evidence that Lotemax is effective for the treatment of postoperative inflammation following ocular surgery for childhood cataract.

The applicant proposed the following text for the Pediatric Use (8.4) sections of the label.

(b) (4)

However, in previous NDAs with similar indications, the proportion of subjects with clearing of anterior chamber inflammation was used as the primary efficacy endpoint. Clearing of anterior chamber inflammation was measured using either the clearing of the ACC (ACC grade of zero) only **or** clearing of the ACC and ACF (grade of zero on both).

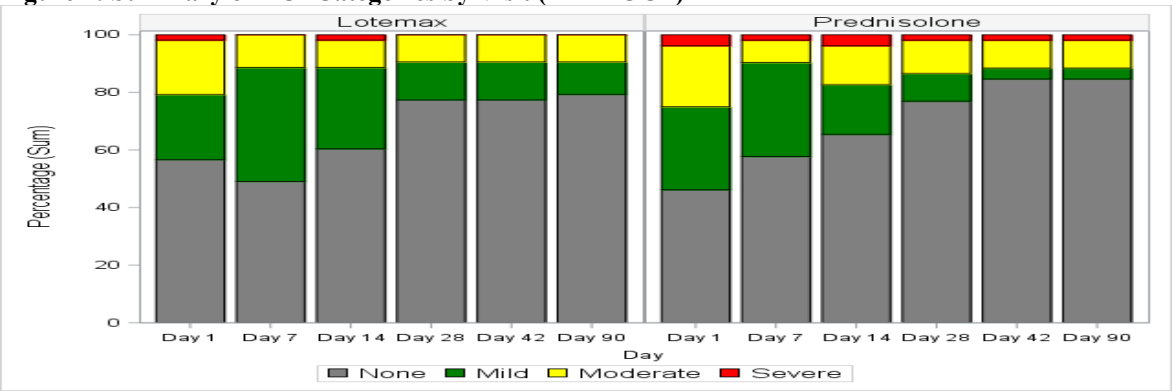
The proportion of subjects with clearing of ACI was one of the secondary efficacy endpoints in this study. Because subjects received rescue therapy due to increased inflammation or an inflammation that did not change while on treatment, it is reasonable to treat subjects who received rescue therapy as treatment failures in the primary efficacy analysis. Therefore, the proportion of subjects with clearing of anterior chamber inflammation without using rescue therapy is an appropriate endpoint to evaluate the efficacy of Lotemax in this study. The efficacy of Lotemax has been established in this study by the analyses results of the primary and several secondary efficacy endpoints including this endpoint. Therefore, to be consistent with previous NDA labeling, and to provide easily interpretable results for prescribing physicians, the statistical review team proposes the following text for Section 14 of the drug labeling.

The safety and effectiveness of LOTEMAX was evaluated in a pediatric study of patients from birth to less than 11 years of age (mean age of 3 years) who were undergoing routine, uncomplicated surgery for childhood cataract. One-hundred seven patients were randomized to receive either LOTEMAX (N=54) or prednisolone acetate ophthalmic suspension 1% (N=53) four times daily for 14 days. At Day 14, the percentage of patients with complete clearing of anterior chamber inflammation was 57% in the LOTEMAX group and 63% in the prednisolone group, with a treatment difference of -7% (95% CI: -26%, 12%).

6 Appendix A: Summary of Efficacy and Safety

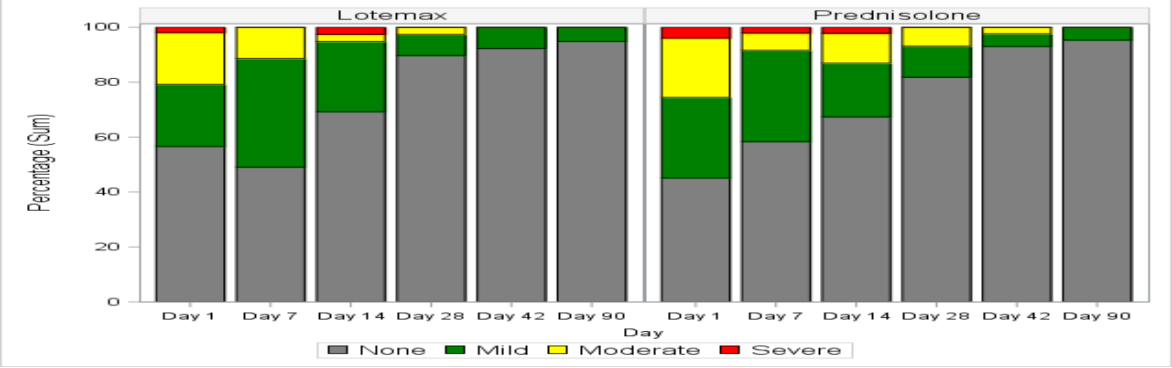
Anterior Chamber inflammation (ACI)

Figure 1: Summary of ACI Categories by Visit (ITT-LOCF)



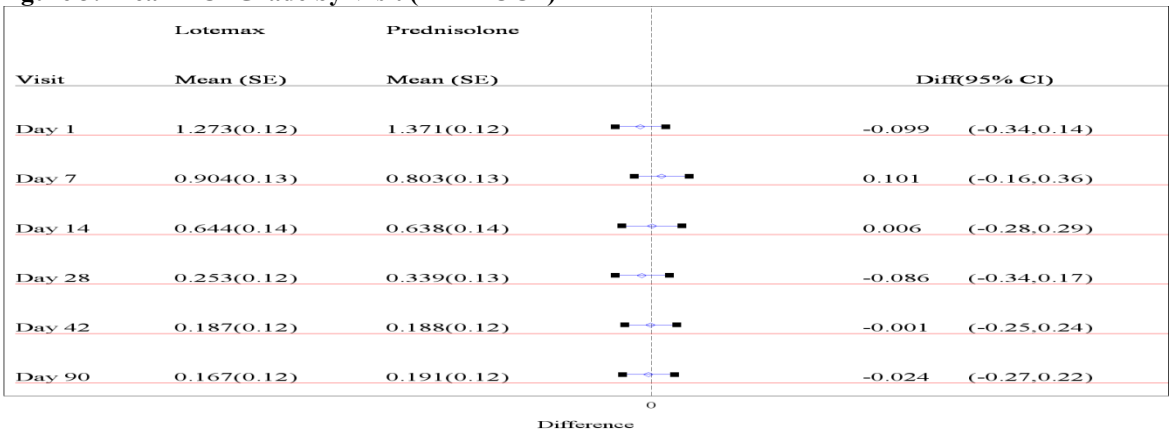
Source: Reviewer's analysis.

Figure 2: Summary of ACI Categories by Visit (ITT-Observed)



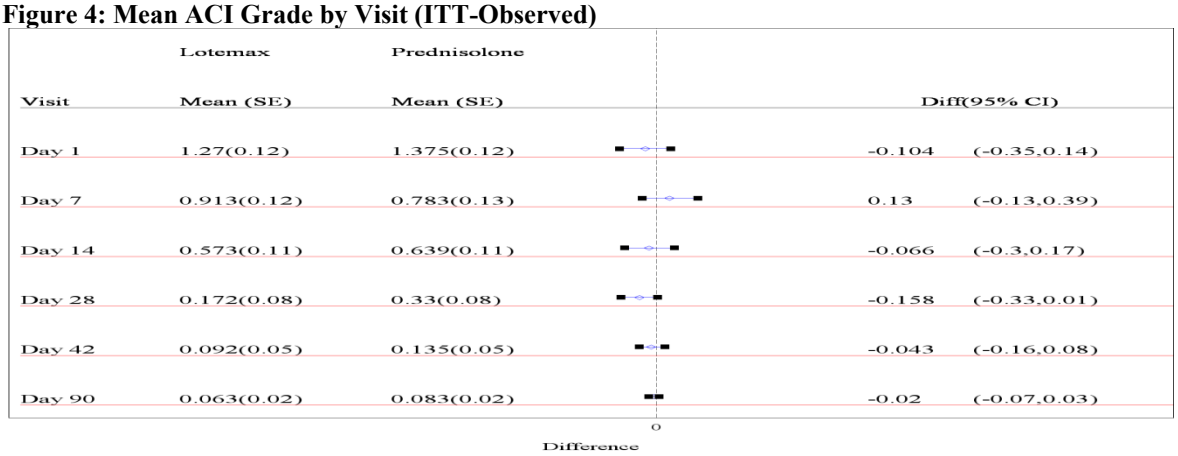
Source: Reviewer's analysis.

Figure 3: Mean ACI Grade by Visit (ITT-LOCF)



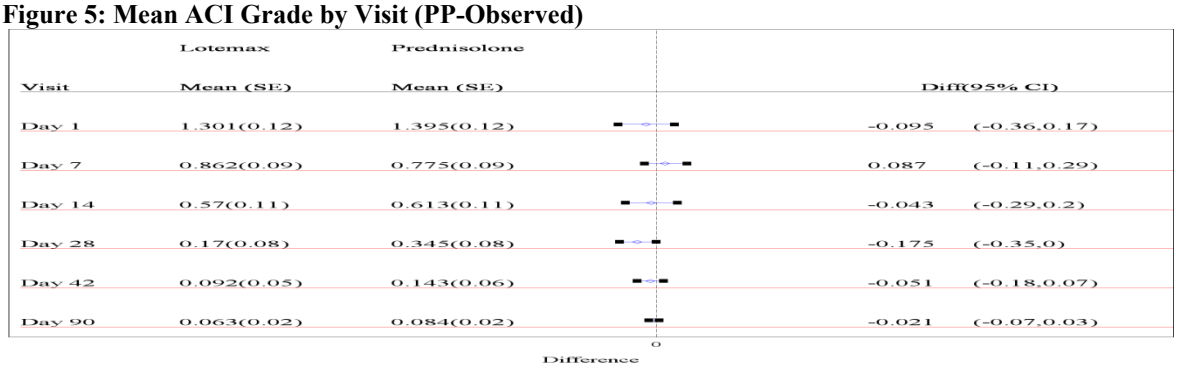
Source: Adapted from Table 14.2.1.1 of the study report. Results for Days 1, 7, 28, 42 and 90 are provided by the reviewer.

Figure 4: Mean ACI Grade by Visit (ITT-Observed)



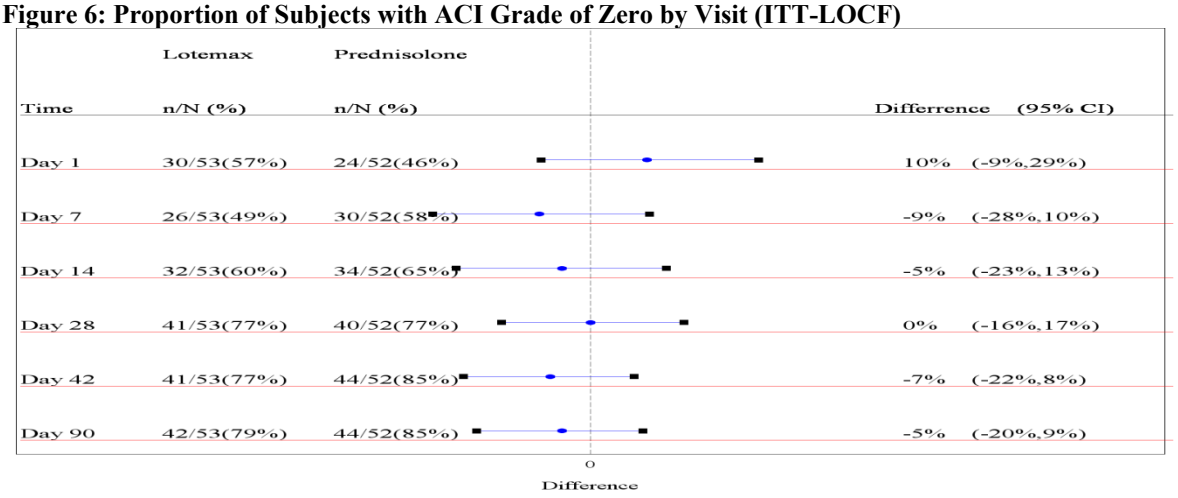
Source: Adapted from Table 14.2.1.3 of the Study report. Results for Days 1, 42 and 90 are provided by the reviewer.

Figure 5: Mean ACI Grade by Visit (PP-Observed)



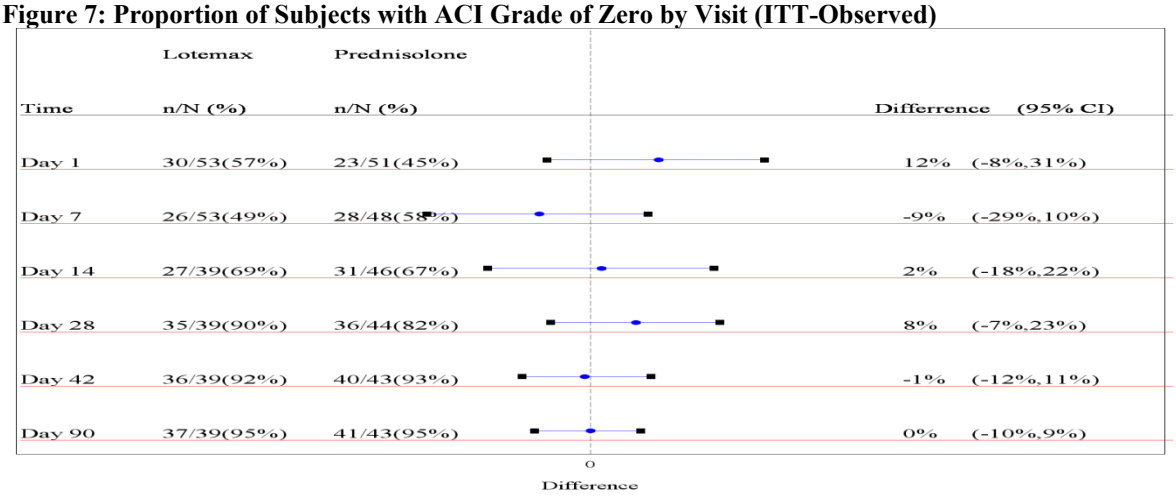
Source: Adapted from Table 14. 2.1.4 of the Study report. Results for Days 1, 42 and 90 are provided by the reviewer.

Figure 6: Proportion of Subjects with ACI Grade of Zero by Visit (ITT-LOCF)



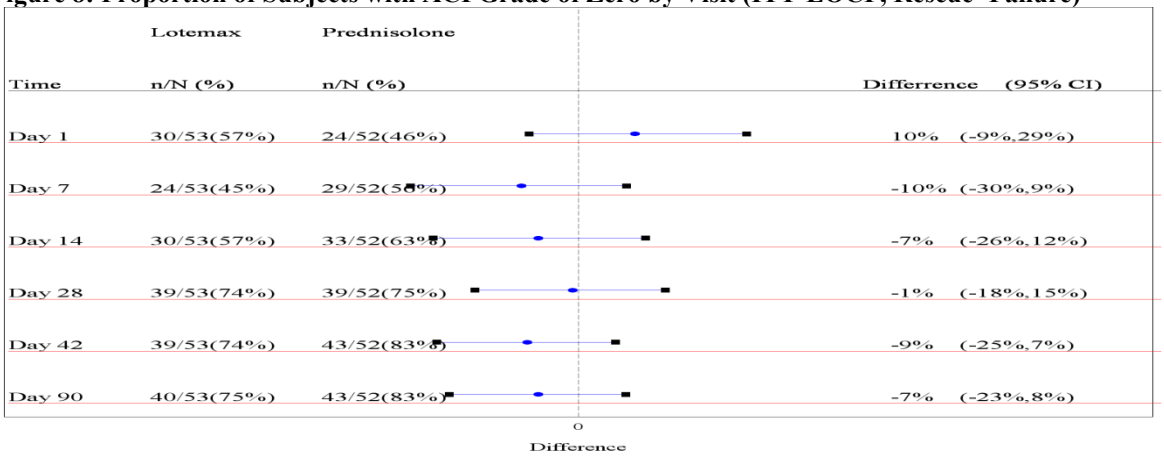
Source: Reviewer's analysis.

Figure 7: Proportion of Subjects with ACI Grade of Zero by Visit (ITT-Observed)



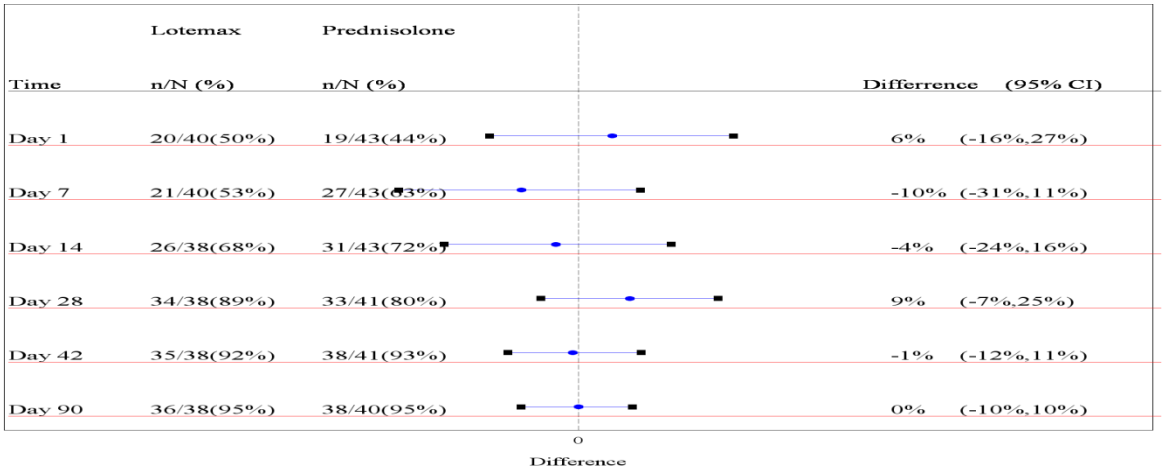
Source: Adapted from Table 14.2.2.1 of the study reports. Results for Days 1, 42 and 90 are provided by the reviewer. The 95% CI for the treatment differences for all visits are calculated by the reviewer

Figure 8: Proportion of Subjects with ACI Grade of Zero by Visit (ITT-LOCF, Rescue=Failure)



Source: Reviewer's analysis.

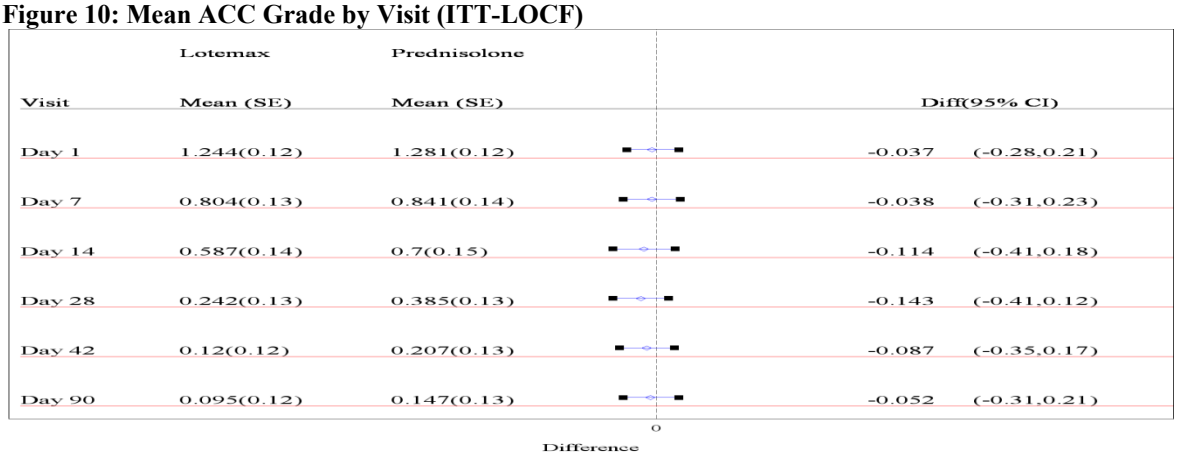
Figure 9: Proportion of Subjects with ACI Grade of Zero by Visit (PP-Observed)



Source: Adapted from Table 14.2.2.2 of the study reports. Results for Days 1, 42 and 90 are provided by the reviewer. The 95% CI for the treatment differences for all visits are calculated by the reviewer

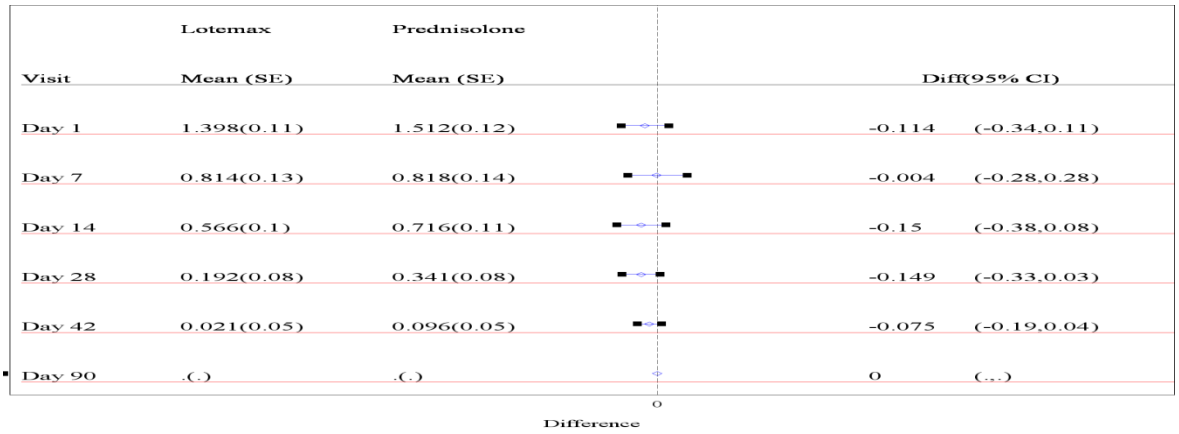
Anterior Chamber Cells (ACC)

Figure 10: Mean ACC Grade by Visit (ITT-LOCF)



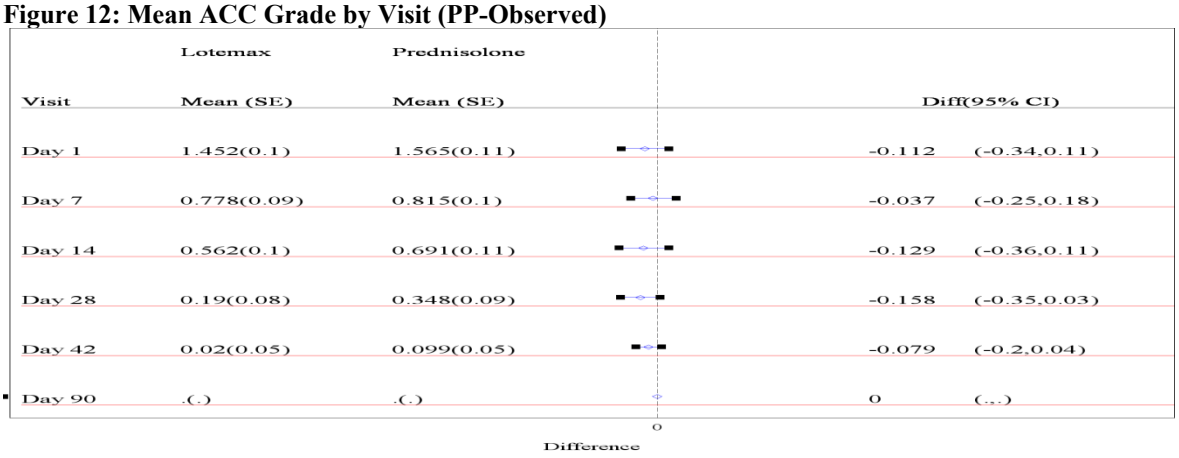
Source: Reviewer's Analysis

Figure 11: Mean ACC Grade by Visit (ITT-Observed)



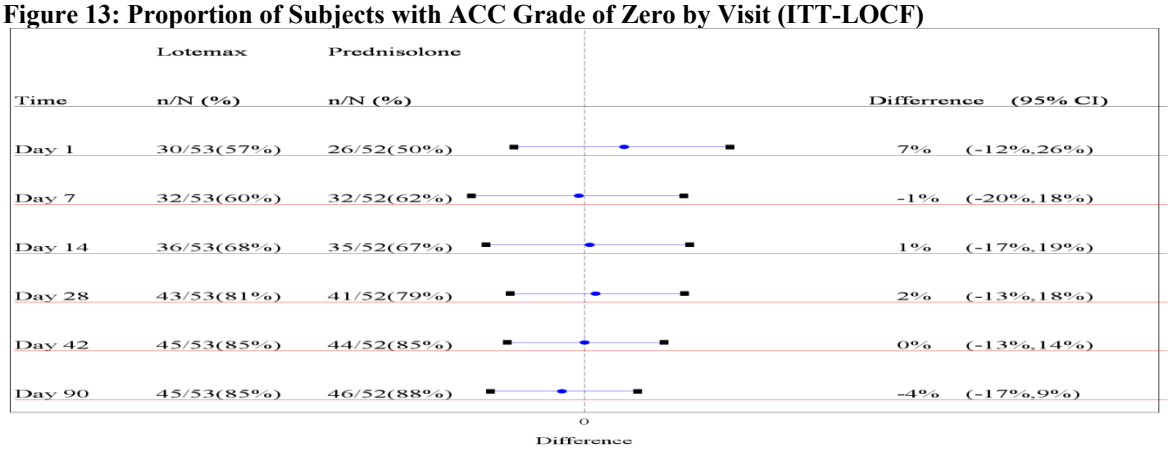
Source: Adapted from Table 14.2.1.9 of the study report. Results for Days 1, 42 and 90 are provided by the reviewer.

Figure 12: Mean ACC Grade by Visit (PP-Observed)



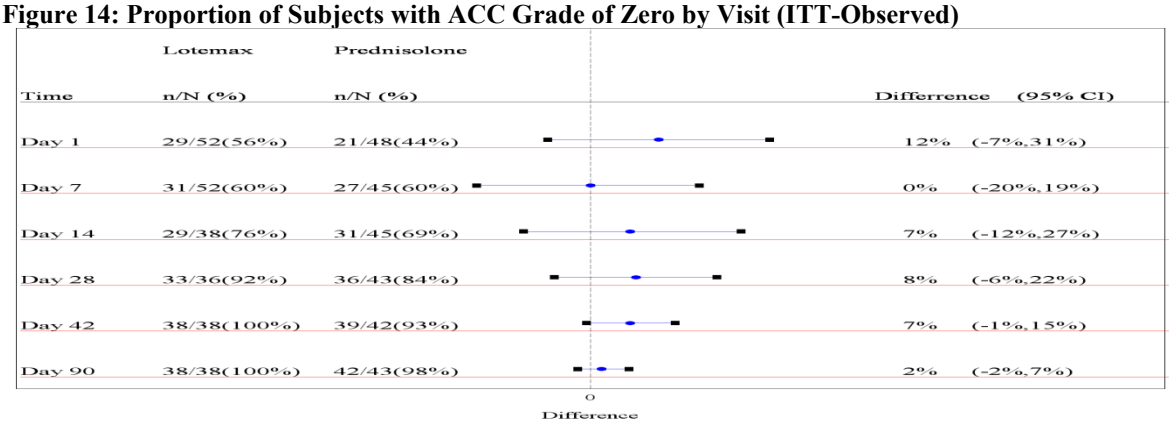
Source: Reviewer's Analysis

Figure 13: Proportion of Subjects with ACC Grade of Zero by Visit (ITT-LOCF)



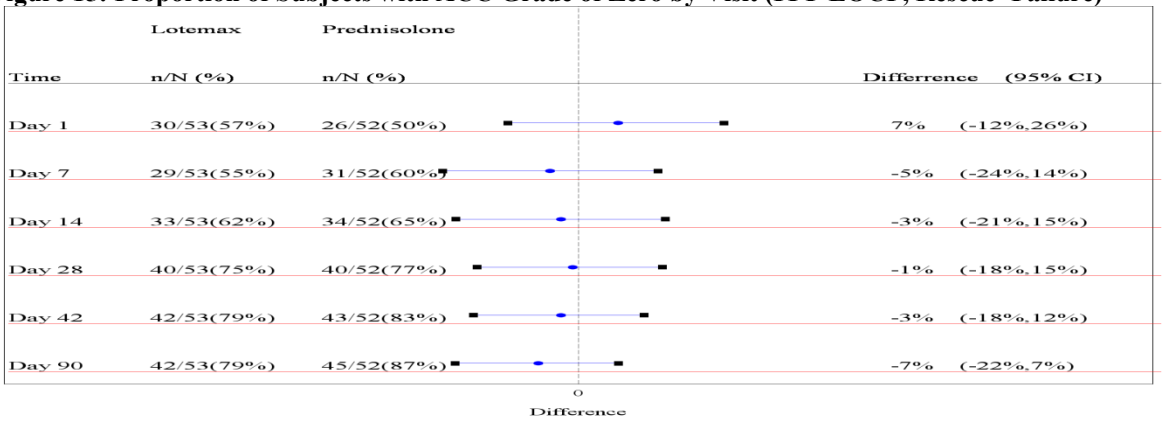
Source: Reviewer's Analysis

Figure 14: Proportion of Subjects with ACC Grade of Zero by Visit (ITT-Observed)



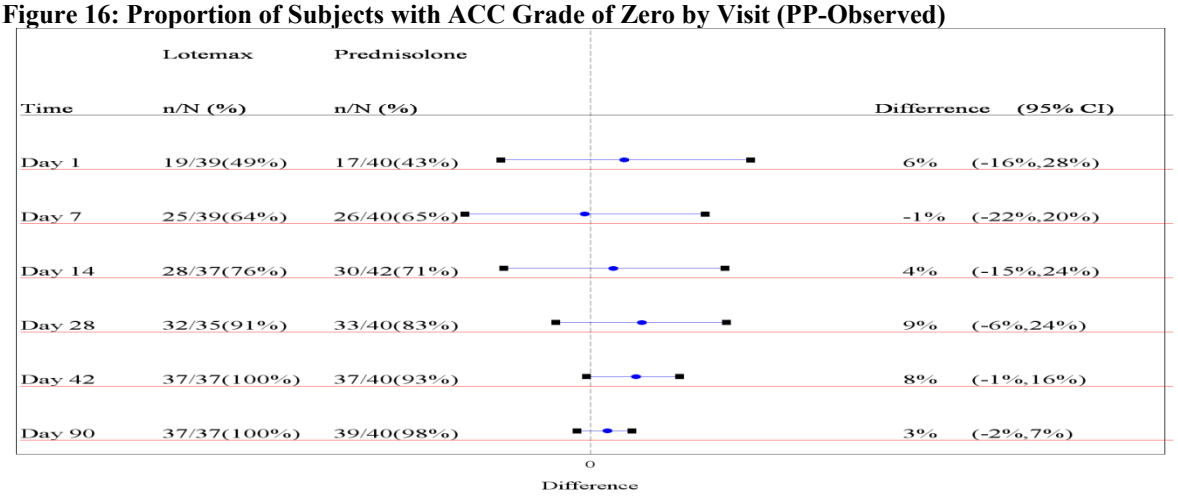
Source: Adapted from Table 14.2.2.1 of the study reports. Results for Days 1, 42 and 90 are provided by the reviewer. The 95% CI for the treatment differences for all visits are calculated by the reviewer.

Figure 15: Proportion of Subjects with ACC Grade of Zero by Visit (ITT-LOCF, Rescue=Failure)



Source: Reviewer's Analysis

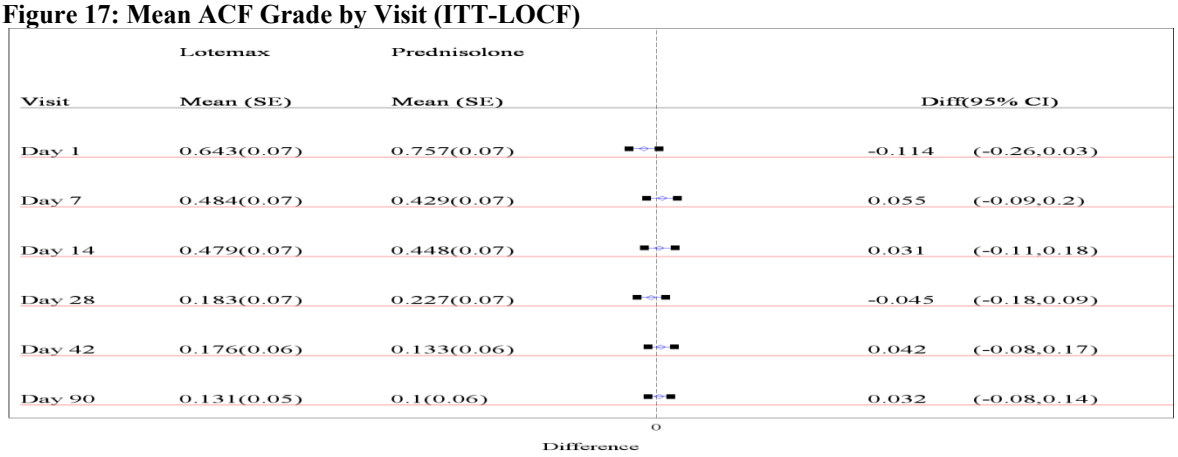
Figure 16: Proportion of Subjects with ACC Grade of Zero by Visit (PP-Observed)



Source: Adapted from Table 14.2.2.2 of the study reports. Results for Days 1, 42 and 90 are provided by the reviewer. The 95% CI for the treatment differences for all visits are calculated by the reviewer.

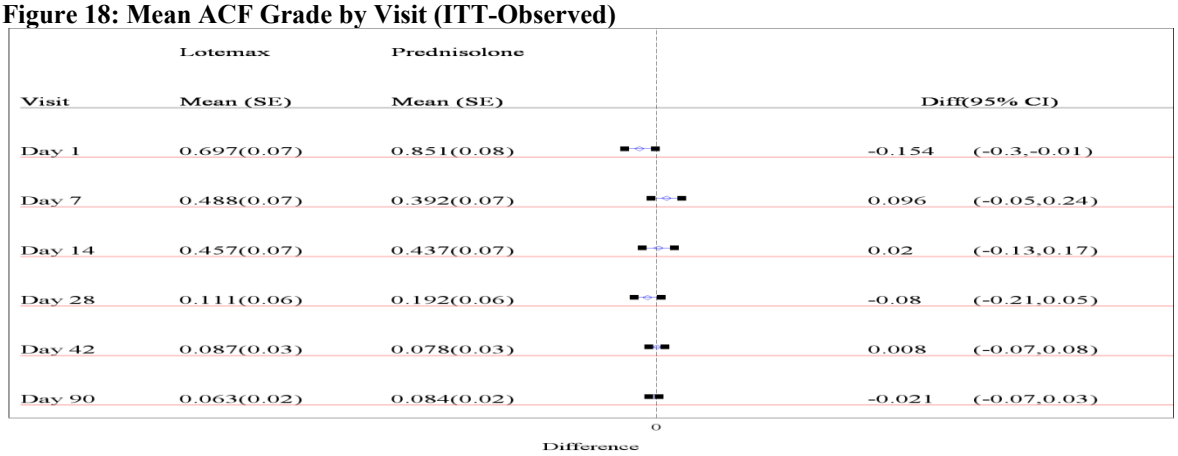
Anterior Chamber Flare (ACF)

Figure 17: Mean ACF Grade by Visit (ITT-LOCF)



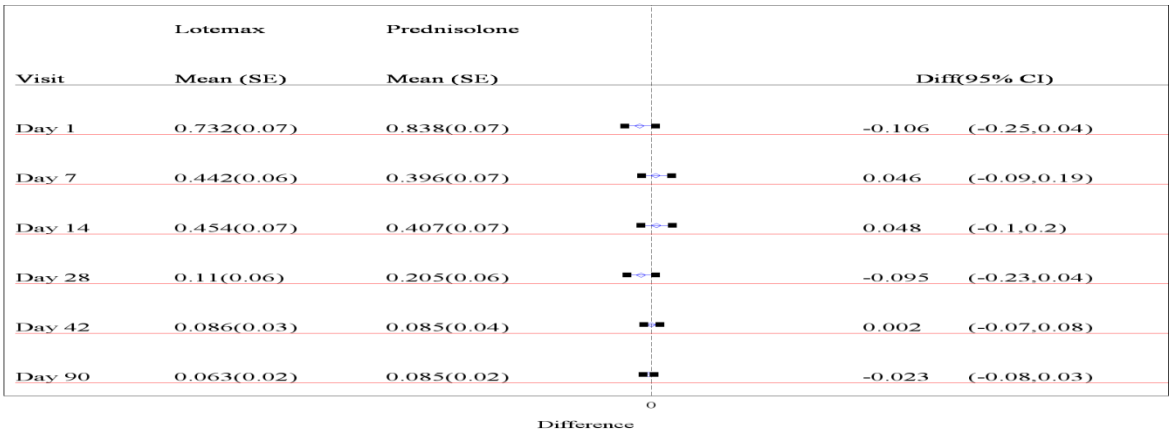
Source: Reviewer's Analysis

Figure 18: Mean ACF Grade by Visit (ITT-Observed)



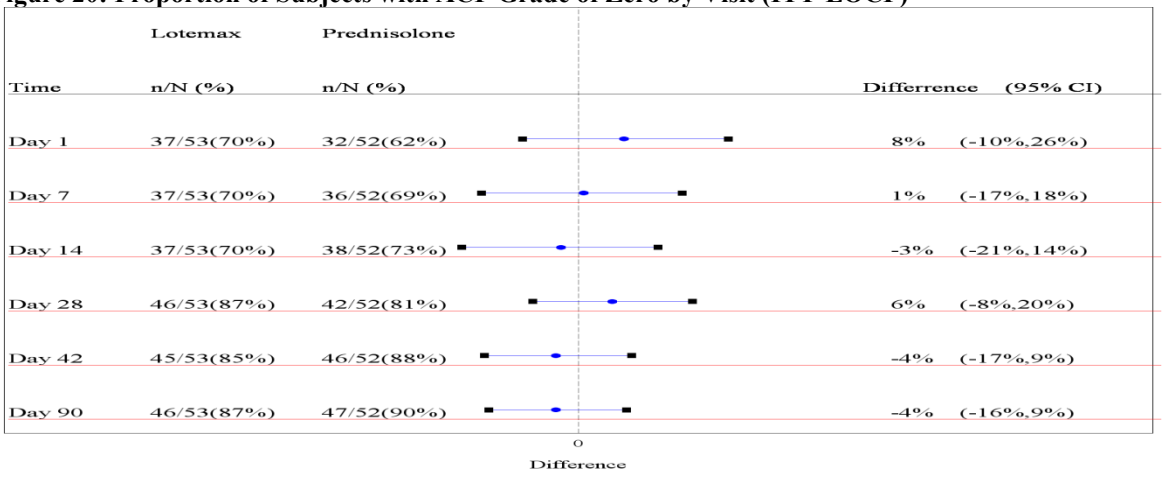
Source: Adapted from Table 14.2.1.9 of the study reports. Results for Days 1, 42 and 90 are provided by the reviewer.

Figure 19: Mean ACF Grade by Visit (PP-Observed)



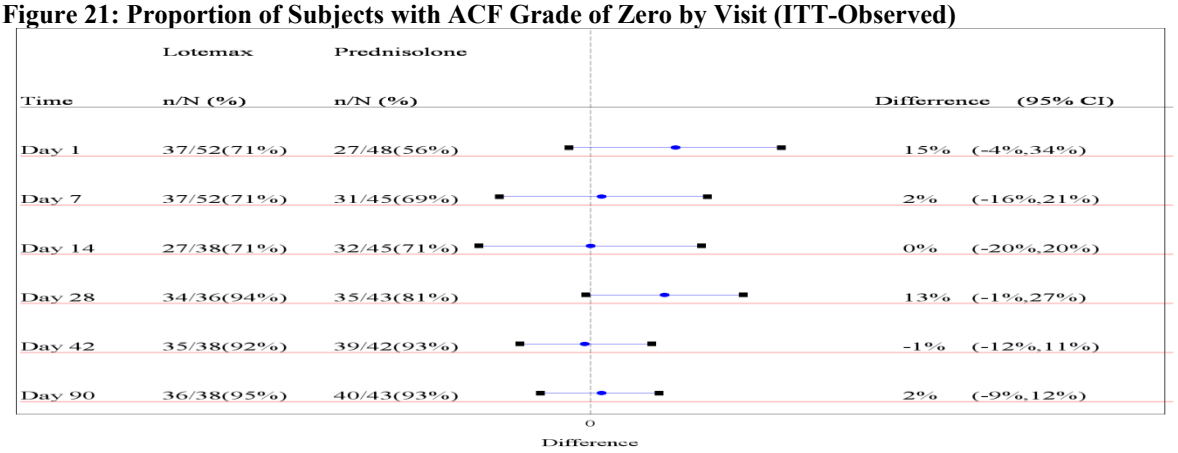
Source: Reviewer's Analysis

Figure 20: Proportion of Subjects with ACF Grade of Zero by Visit (ITT-LOCF)



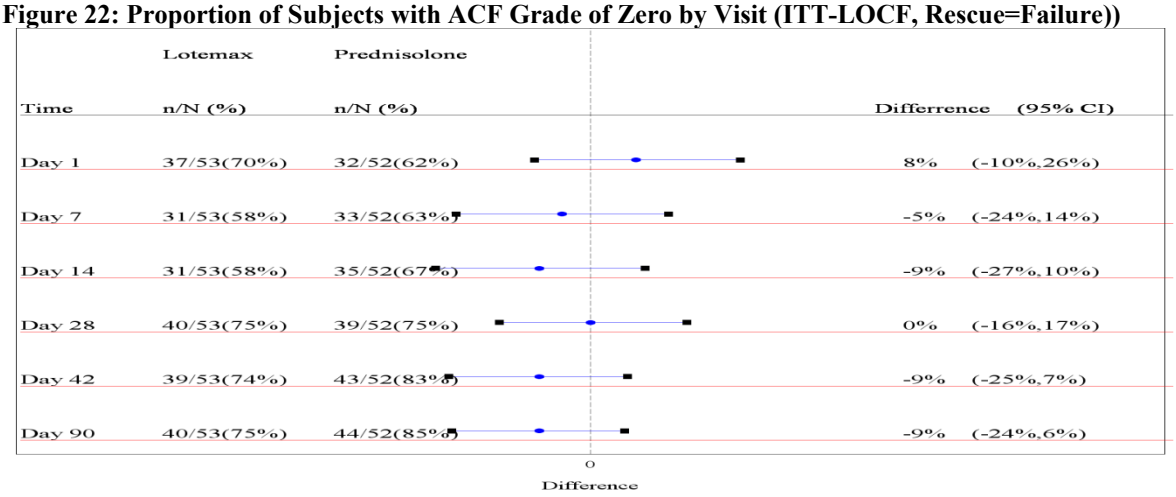
Source: Reviewer's Analysis

Figure 21: Proportion of Subjects with ACF Grade of Zero by Visit (ITT-Observed)



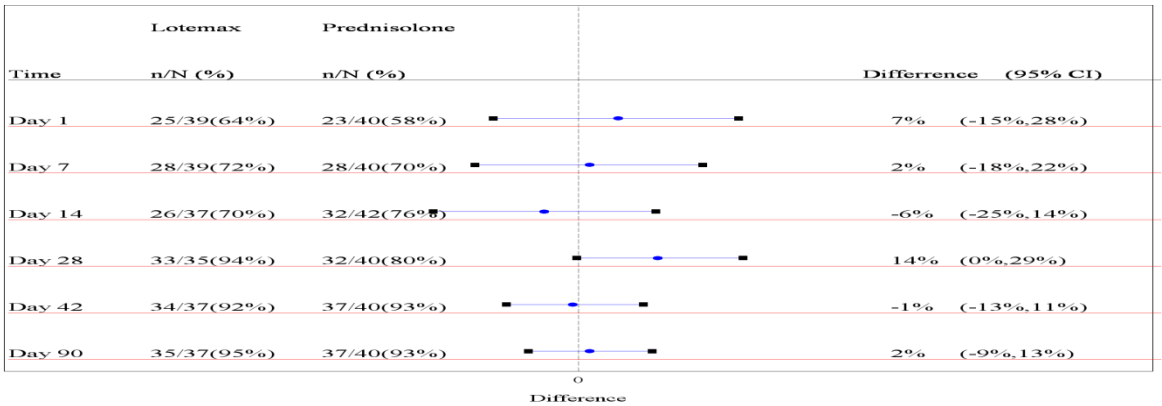
Source: Adapted from Table 14.2.2.1 of the study report. Results for Days 1, 42 and 90 are provided by the reviewer. The 95% CI for the treatment differences for all visits are calculated by the reviewer.

Figure 22: Proportion of Subjects with ACF Grade of Zero by Visit (ITT-LOCF, Rescue=Failure))



Source: Reviewer's Analysis

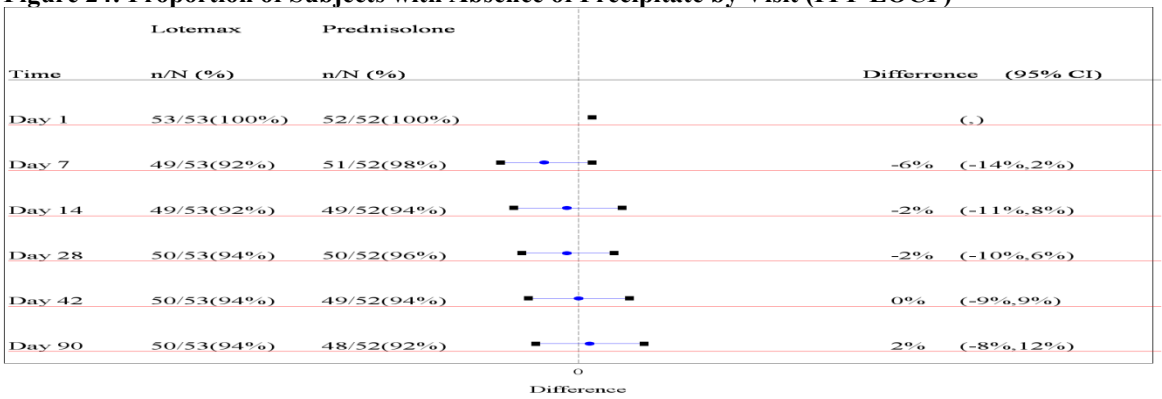
Figure 23: Proportion of Subjects with ACF Grade of Zero by Visit (PP-Observed)



Source: Adapted from Table 14.2.2.2 of the study report. Results for Days 1, 42 and 90 are provided by the reviewer. The 95% CI for the treatment differences for all visits are calculated by the reviewer.

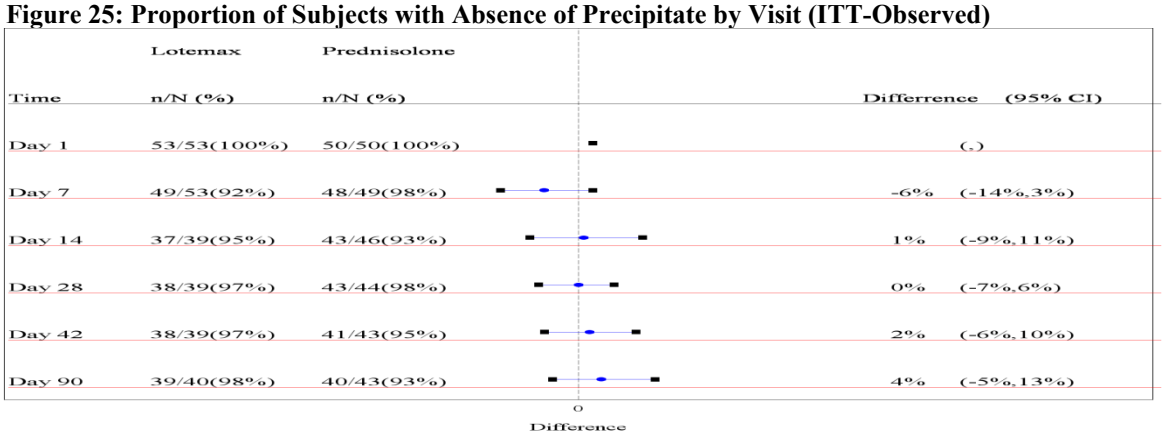
Precipitate

Figure 24: Proportion of Subjects with Absence of Precipitate by Visit (ITT-LOCF)



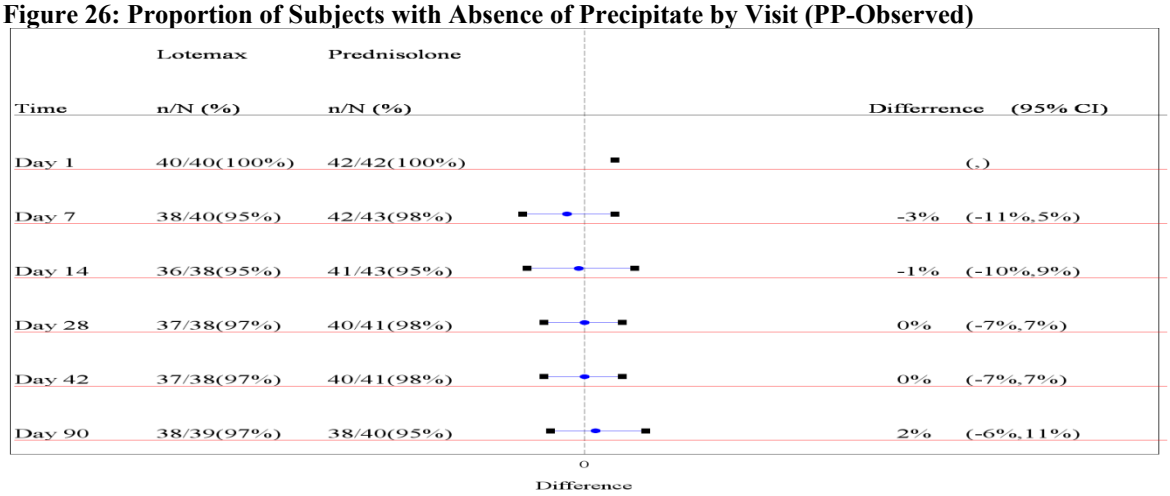
Source: Reviewer's Analysis

Figure 25: Proportion of Subjects with Absence of Precipitate by Visit (ITT-Observed)



Source: Adapted from Table 14.2.4.1 of the study report. Results for Days 1, 42 and 90 are provided by the reviewer

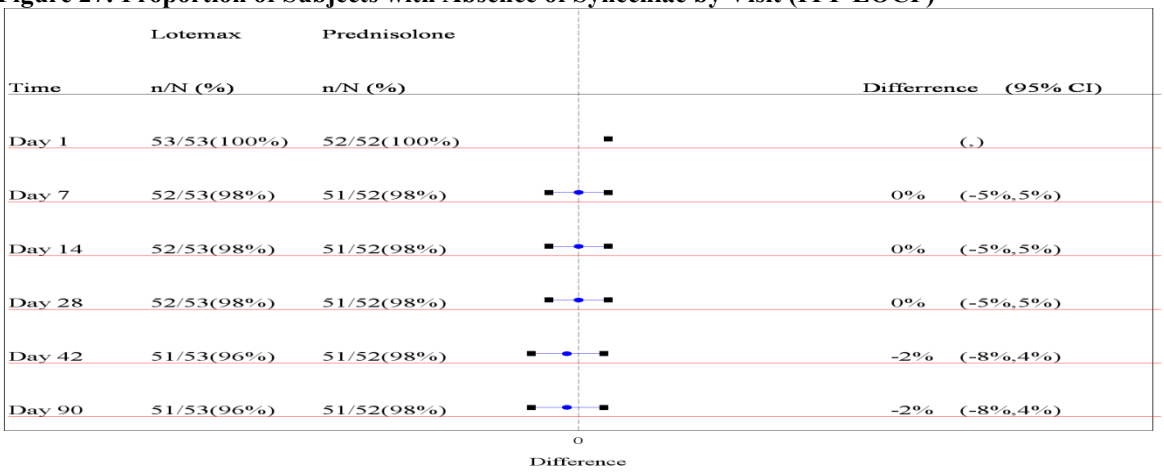
Figure 26: Proportion of Subjects with Absence of Precipitate by Visit (PP-Observed)



Source: Adapted from Table 14.2.4.2 of the study report. Results for Days 1, 42 and 90 are provided by the reviewer

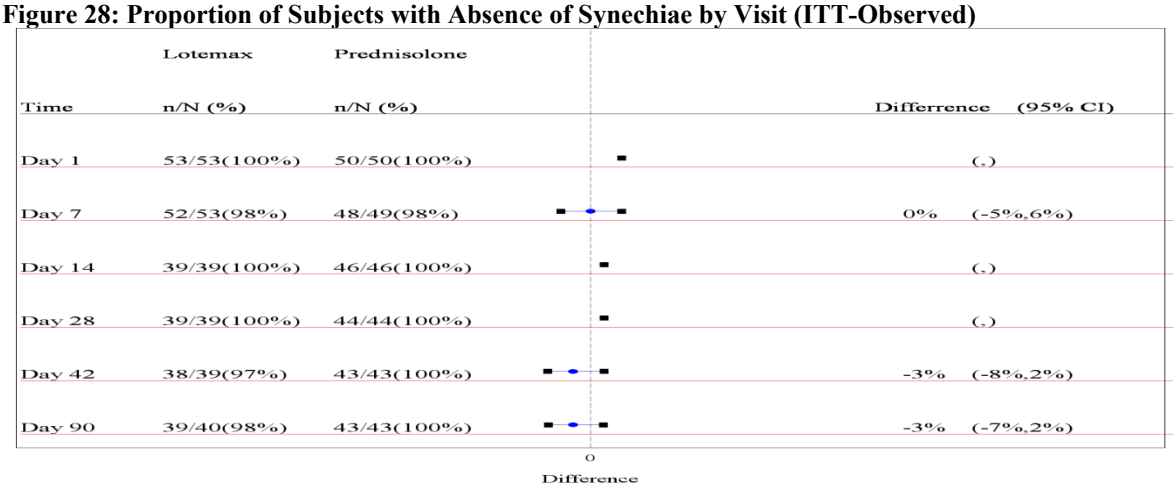
Synechiae

Figure 27: Proportion of Subjects with Absence of Synechiae by Visit (ITT-LOCF)



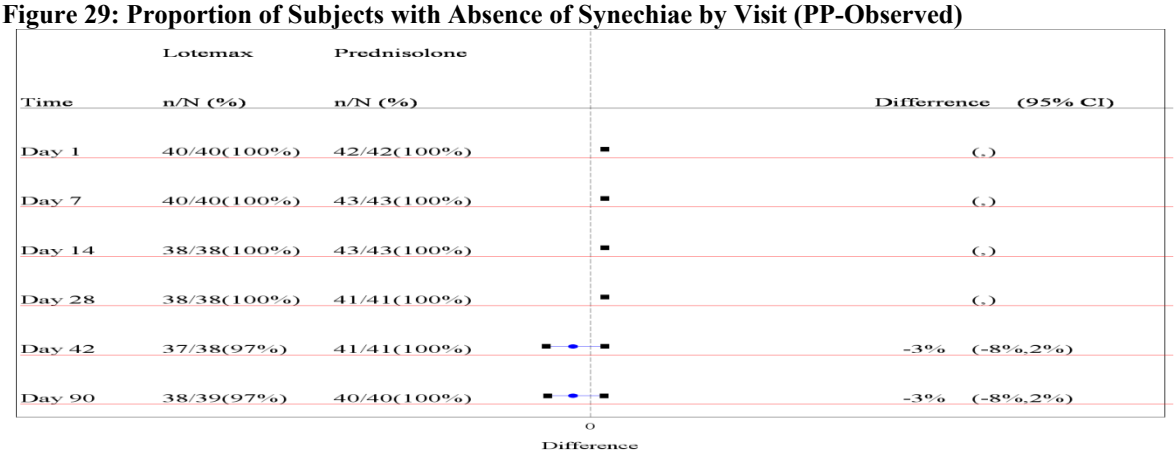
Source: Reviewer's Analysis

Figure 28: Proportion of Subjects with Absence of Synechiae by Visit (ITT-Observed)



Source: Adapted from Table 14.2.3.1 of the study report. Results for Days 1, 42 and 90 are provided by the reviewer

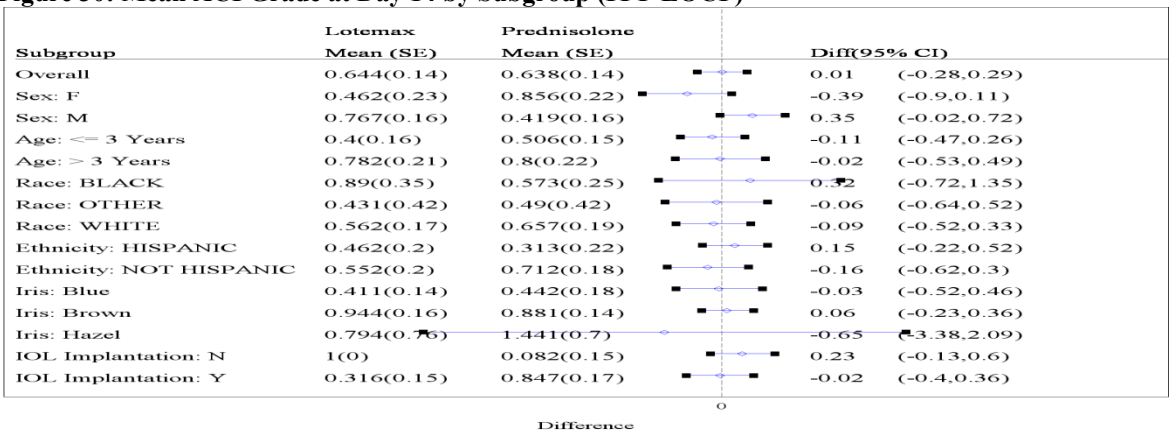
Figure 29: Proportion of Subjects with Absence of Synechiae by Visit (PP-Observed)



Source: Adapted from Table 14.2.3.2 of the study report. Results for Days 1, 42 and 90 are provided by the reviewer

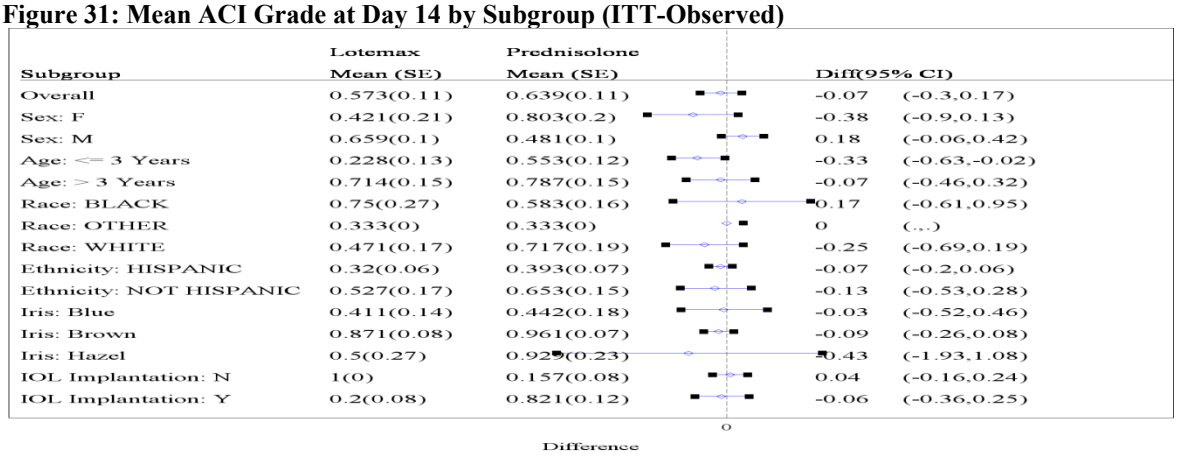
Subgroup Results (ACI, ACC and ACF)

Figure 30: Mean ACI Grade at Day 14 by Subgroup (ITT-LOCF)



Source: Reviewer's Analysis

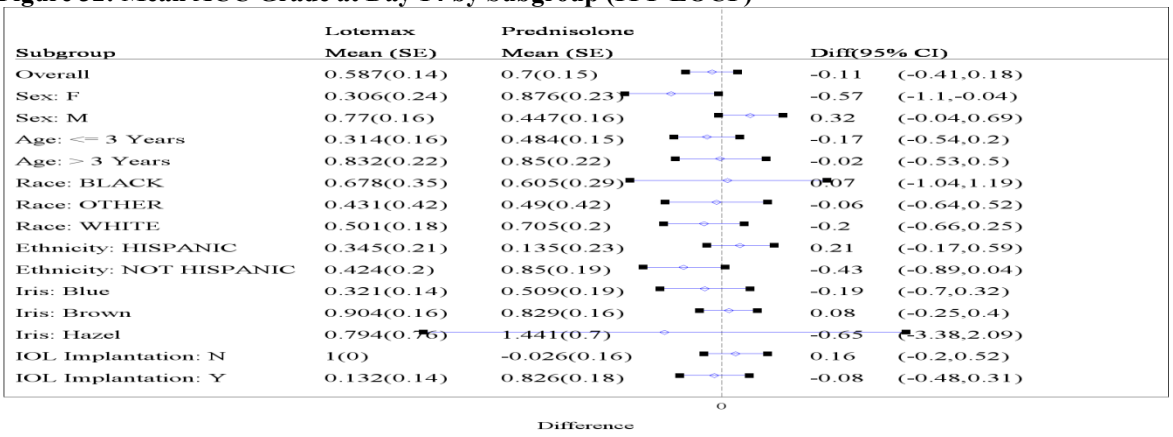
Figure 31: Mean ACI Grade at Day 14 by Subgroup (ITT-Observed)



Subgroup	Lotemax Mean (SE)	Prednisolone Mean (SE)	Diff(95% CI)	
Overall	0.573(0.11)	0.639(0.11)	-0.07	(-0.3,0.17)
Sex: F	0.421(0.21)	0.803(0.2)	-0.38	(-0.9,0.13)
Sex: M	0.659(0.1)	0.481(0.1)	0.18	(-0.06,0.42)
Age: <= 3 Years	0.228(0.13)	0.553(0.12)	-0.33	(-0.63,-0.02)
Age: > 3 Years	0.714(0.15)	0.787(0.15)	-0.07	(-0.46,0.32)
Race: BLACK	0.75(0.27)	0.583(0.16)	0.17	(-0.61,0.95)
Race: OTHER	0.333(0)	0.333(0)	0	(.,.)
Race: WHITE	0.471(0.17)	0.717(0.19)	-0.25	(-0.69,0.19)
Ethnicity: HISPANIC	0.32(0.06)	0.393(0.07)	-0.07	(-0.2,0.06)
Ethnicity: NOT HISPANIC	0.527(0.17)	0.653(0.15)	-0.13	(-0.53,0.28)
Iris: Blue	0.411(0.14)	0.442(0.18)	-0.03	(-0.52,0.46)
Iris: Brown	0.871(0.08)	0.961(0.07)	-0.09	(-0.26,0.08)
Iris: Hazel	0.5(0.27)	0.929(0.23)	-0.43	(-1.93,1.08)
IOL Implantation: N	1(0)	0.157(0.08)	0.04	(-0.16,0.24)
IOL Implantation: Y	0.2(0.08)	0.821(0.12)	-0.06	(-0.36,0.25)

Source: Adapted from Table 14.2.1.5, Table 14.2.1.6, Table 14.2.1.7 and Table 14.2.1.8 of the study report.

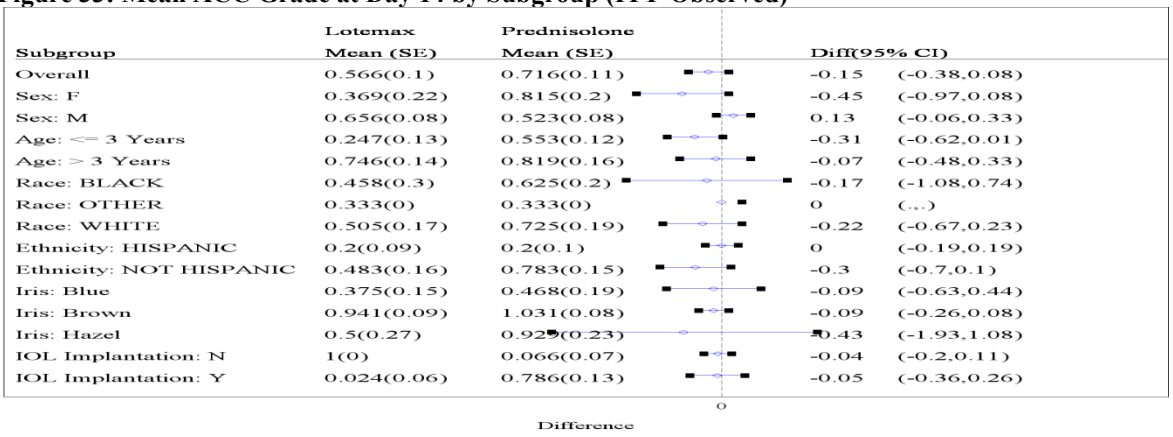
Figure 32: Mean ACC Grade at Day 14 by Subgroup (ITT-LOCF)



Subgroup	Lotemax Mean (SE)	Prednisolone Mean (SE)	Diff(95% CI)	
Overall	0.587(0.14)	0.7(0.15)	-0.11	(-0.41,0.18)
Sex: F	0.306(0.24)	0.876(0.23)	-0.57	(-1.1,-0.04)
Sex: M	0.77(0.16)	0.447(0.16)	0.32	(-0.04,0.69)
Age: <= 3 Years	0.314(0.16)	0.484(0.15)	-0.17	(-0.54,0.2)
Age: > 3 Years	0.832(0.22)	0.85(0.22)	-0.02	(-0.53,0.5)
Race: BLACK	0.678(0.35)	0.605(0.29)	0.07	(-1.04,1.19)
Race: OTHER	0.431(0.42)	0.49(0.42)	-0.06	(-0.64,0.52)
Race: WHITE	0.501(0.18)	0.705(0.2)	-0.2	(-0.66,0.25)
Ethnicity: HISPANIC	0.345(0.21)	0.135(0.23)	0.21	(-0.17,0.59)
Ethnicity: NOT HISPANIC	0.424(0.2)	0.85(0.19)	-0.43	(-0.89,0.04)
Iris: Blue	0.321(0.14)	0.509(0.19)	-0.19	(-0.7,0.32)
Iris: Brown	0.904(0.16)	0.829(0.16)	0.08	(-0.25,0.4)
Iris: Hazel	0.794(0.76)	1.441(0.7)	-0.65	(-3.38,2.09)
IOL Implantation: N	1(0)	-0.026(0.16)	0.16	(-0.2,0.52)
IOL Implantation: Y	0.132(0.14)	0.826(0.18)	-0.08	(-0.48,0.31)

Source: Reviewer's Analysis

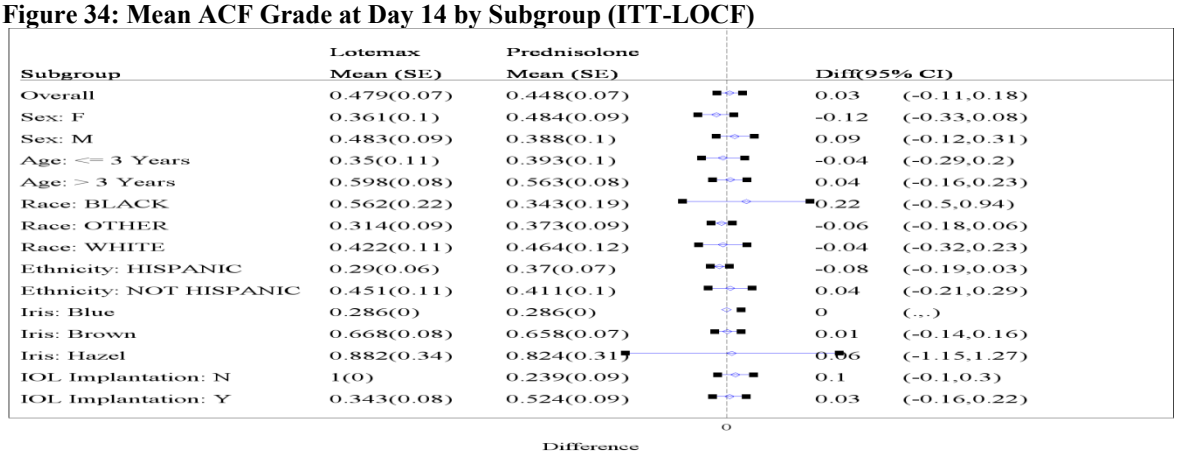
Figure 33: Mean ACC Grade at Day 14 by Subgroup (ITT-Observed)



Subgroup	Lotemax Mean (SE)	Prednisolone Mean (SE)	Diff(95% CI)	
Overall	0.566(0.1)	0.716(0.11)	-0.15	(-0.38,0.08)
Sex: F	0.369(0.22)	0.815(0.2)	-0.45	(-0.97,0.08)
Sex: M	0.656(0.08)	0.523(0.08)	0.13	(-0.06,0.33)
Age: <= 3 Years	0.247(0.13)	0.553(0.12)	-0.31	(-0.62,0.01)
Age: > 3 Years	0.746(0.14)	0.819(0.16)	-0.07	(-0.48,0.33)
Race: BLACK	0.458(0.3)	0.625(0.2)	-0.17	(-1.08,0.74)
Race: OTHER	0.333(0)	0.333(0)	0	(.,.)
Race: WHITE	0.505(0.17)	0.725(0.19)	-0.22	(-0.67,0.23)
Ethnicity: HISPANIC	0.2(0.09)	0.2(0.1)	0	(-0.19,0.19)
Ethnicity: NOT HISPANIC	0.483(0.16)	0.783(0.15)	-0.3	(-0.7,0.1)
Iris: Blue	0.375(0.15)	0.468(0.19)	-0.09	(-0.63,0.44)
Iris: Brown	0.941(0.09)	1.031(0.08)	-0.09	(-0.26,0.08)
Iris: Hazel	0.5(0.27)	0.929(0.23)	-0.43	(-1.93,1.08)
IOL Implantation: N	1(0)	0.066(0.07)	-0.04	(-0.2,0.11)
IOL Implantation: Y	0.024(0.06)	0.786(0.13)	-0.05	(-0.36,0.26)

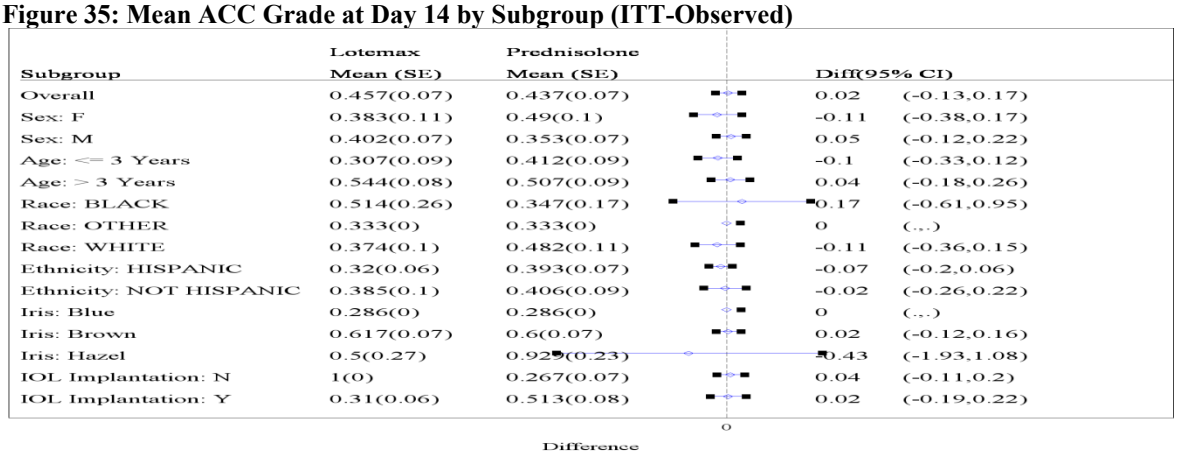
Source: Adapted from Table 14.2.1.5, Table 14.2.1.6, Table 14.2.1.7 and Table 14.2.1.8 of the study report.

Figure 34: Mean ACF Grade at Day 14 by Subgroup (ITT-LOCF)



Source: Reviewer's Analysis

Figure 35: Mean ACC Grade at Day 14 by Subgroup (ITT-Observed)



Source: Adapted from Table 14.2.1.5, Table 14.2.1.6, Table 14.2.1.7 and Table 14.2.1.8 of the study report.

7 Appendix B: Efficacy Outcomes of Selected Subjects

Table 12: Efficacy Outcomes for Subjects whose Inflammation was measured using a Penlight

USUBJID	TRT01P	Day	ACC	ACF	ACI	ITTFL	PPROTFL	SAFFL	Rescue
(b) (6)	Prednisolone	0	0	0	0	Y	Y	Y	No
	Prednisolone	1	2	1	2	Y	Y	Y	No
	Prednisolone	7	.	.	0	Y	Y	Y	No
	Prednisolone	14	2	1	2	Y	Y	Y	No
	Prednisolone	28	1	1	1	Y	Y	Y	No
	Prednisolone	42	2	0	2	Y	Y	Y	No
	Prednisolone	90	.	.	.	Y	Y	Y	No
	Lotemax	0	0	0	0	Y	Y	Y	No
	Lotemax	1	0	0	0	Y	Y	Y	No
	Lotemax	7	0	0	0	Y	Y	Y	No
	Lotemax	14	0	0	0	Y	Y	Y	No
	Lotemax	28	.	.	0	Y	Y	Y	No
	Lotemax	42	.	.	0	Y	Y	Y	No
	Lotemax	90	.	.	0	Y	Y	Y	No
	Prednisolone	0	.	.	0	Y	Y	Y	No
	Prednisolone	1	.	.	0	Y	Y	Y	No
	Prednisolone	7	.	.	0	Y	Y	Y	No
	Prednisolone	14	.	.	0	Y	Y	Y	No
	Prednisolone	28	.	.	0	Y	Y	Y	No
	Prednisolone	42	.	.	0	Y	Y	Y	No
	Prednisolone	90	.	.	0	Y	Y	Y	No
	Prednisolone	0	0	0	0	Y	Y	Y	No
	Prednisolone	1	0	0	0	Y	Y	Y	No
	Prednisolone	7	.	.	0	Y	Y	Y	No
	Prednisolone	14	0	0	0	Y	Y	Y	No
	Prednisolone	28	0	0	0	Y	Y	Y	No
	Prednisolone	42	0	0	0	Y	Y	Y	No
	Prednisolone	90	0	0	0	Y	Y	Y	No
	Prednisolone	0	0	0	0	Y	Y	Y	No
	Prednisolone	1	.	.	0	Y	Y	Y	No
	Prednisolone	7	0	0	0	Y	Y	Y	No
	Prednisolone	14	0	0	0	Y	Y	Y	No
	Prednisolone	28	0	0	0	Y	Y	Y	No
	Prednisolone	42	0	0	0	Y	Y	Y	No
	Prednisolone	90	0	0	0	Y	Y	Y	No
	Lotemax	0	0	1	1	Y	Y	Y	No
	Lotemax	1	.	.	0	Y	Y	Y	No
	Lotemax	7	.	.	1	Y	Y	Y	No

	Lotemax	14	.	.	0	Y	Y	Y	No
	Lotemax	28	.	.	0	Y	Y	Y	No
	Lotemax	42	0	1	1	Y	Y	Y	No
	Lotemax	90	0	1	1	Y	Y	Y	No
	Lotemax	0	0	0	0	Y	Y	Y	No
	Lotemax	1	0	0	0	Y	Y	Y	No
	Lotemax	7	0	0	0	Y	Y	Y	No
	Lotemax	14	0	0	0	Y	Y	Y	No
(b) (6)	Lotemax	28	.	.	0	Y	Y	Y	No
	Lotemax	42	0	0	0	Y	Y	Y	No
	Lotemax	90	0	0	0	Y	Y	Y	No
	Prednisolone	0	0	0	0	Y	Y	Y	No
	Prednisolone	1	.	.	2	Y	Y	Y	No
	Prednisolone	7	0	0	0	Y	Y	Y	No
	Prednisolone	14	0	0	0	Y	Y	Y	No
	Prednisolone	28	0	0	0	Y	Y	Y	No
	Prednisolone	42	0	0	0	Y	Y	Y	No
	Prednisolone	90	0	0	0	Y	Y	Y	No
	Prednisolone	0	0	0	0	Y	Y	Y	No
	Prednisolone	1	0	0	0	Y	Y	Y	No
	Prednisolone	7	.	.	0	Y	Y	Y	No
	Prednisolone	14	0	0	0	Y	Y	Y	No
	Prednisolone	28	0	0	0	Y	Y	Y	No
	Prednisolone	42	0	0	0	Y	Y	Y	No
	Prednisolone	90	0	0	0	Y	Y	Y	No
	Prednisolone	0	0	0	0	Y	Y	Y	No
	Prednisolone	1	.	.	2	Y	Y	Y	No
	Prednisolone	7	1	0	1	Y	Y	Y	No
	Prednisolone	14	1	0	1	Y	Y	Y	No
	Prednisolone	28	0	0	0	Y	Y	Y	No
	Prednisolone	42	0	0	0	Y	Y	Y	No
	Prednisolone	90	0	0	0	Y	Y	Y	No
	Prednisolone	0	0	0	0	Y	Y	Y	No
	Prednisolone	1	1	1	1	Y	Y	Y	No
	Prednisolone	7	1	1	1	Y	Y	Y	No
	Prednisolone	14	.	.	0	Y	Y	Y	No
	Prednisolone	28	.	.	0	Y	Y	Y	No
	Prednisolone	42	.	.	0	Y	Y	Y	No
	Prednisolone	90	0	0	0	Y	Y	Y	No

Source: Listings 16.2.4 of the applicant's study reports. TRT01P: Planned treatment.

Table 13: Efficacy Outcomes for Subjects Who Received the Opposite Treatment

USUBJID	TRT01P	TRT01A	Day	ACC	ACF	ACI	ITTFL	PPROTFL	SAFFL	Rescue
	Lotemax	Prednisolone	0	0	0	0	Y	N	Y	No
	Lotemax	Prednisolone	1	0	0	0	Y	N	Y	No
	Lotemax	Prednisolone	7	0	0	0	Y	N	Y	No
	Lotemax	Prednisolone	14	0	0	0	Y	N	Y	No
	Lotemax	Prednisolone	28	0	0	0	Y	N	Y	No
	Lotemax	Prednisolone	42	0	0	0	Y	N	Y	No
	Lotemax	Prednisolone	90	0	0	0	Y	N	Y	No
(b) (6)	Prednisolone	Lotemax	0	0	0	0	Y	N	Y	Yes
	Prednisolone	Lotemax	1	0	0	0	Y	N	Y	Yes
	Prednisolone	Lotemax	7	.	.	.	Y	N	Y	Yes
	Prednisolone	Lotemax	14	.	.	.	Y	N	Y	Yes
	Prednisolone	Lotemax	28	.	.	.	Y	N	Y	Yes
	Prednisolone	Lotemax	42	.	.	.	Y	N	Y	Yes
	Prednisolone	Lotemax	90	.	.	.	Y	N	Y	Yes

Source: Adapted from Listings 16.2.4 of the applicant's study reports. TRT01P: Planned treatment. TRT01A: Actual treatment received.

Table 14: Efficacy Outcomes for Subjects Who Received Rescue Therapy

USUBJID	TRT01P	TRT01A	Day	ACC	ACF	ACI	ITTFL	PPROTFL	SAFFL	Rescue Day
	Prednisolone	Prednisolone	0	0	1	1	Y	Y	Y	14
	Prednisolone	Prednisolone	1	1	1	1	Y	Y	Y	14
	Prednisolone	Prednisolone	7	0	1	1	Y	Y	Y	14
	Prednisolone	Prednisolone	14	2	2	2	Y	Y	Y	14
	Prednisolone	Prednisolone	28	.	.	.	Y	Y	Y	14
(b) (6)	Prednisolone	Prednisolone	42	.	.	.	Y	Y	Y	14
	Prednisolone	Prednisolone	90	.	.	.	Y	Y	Y	14
	Prednisolone	Prednisolone	0	0	1	1	Y	Y	Y	28
	Prednisolone	Prednisolone	1	1	2	2	Y	Y	Y	28
	Prednisolone	Prednisolone	7	1	1	1	Y	Y	Y	28
	Prednisolone	Prednisolone	14	1	1	1	Y	Y	Y	28
	Prednisolone	Prednisolone	28	2	1	2	Y	Y	Y	28
	Prednisolone	Prednisolone	42	.	.	.	Y	Y	Y	28
	Prednisolone	Prednisolone	90	.	.	.	Y	Y	Y	28
	Lotemax	Lotemax	0	0	1	1	Y	N	Y	7
	Lotemax	Lotemax	1	2	1	2	Y	N	Y	7
	Lotemax	Lotemax	7	0	2	2	Y	N	Y	7
	Lotemax	Lotemax	14	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	28	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	42	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	90	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	0	0	1	1	Y	Y	Y	28
	Lotemax	Lotemax	1	1	1	1	Y	Y	Y	28

	Lotemax	Lotemax	7	0	1	1	Y	Y	Y	28
	Lotemax	Lotemax	14	3	2	3	Y	Y	Y	28
	Lotemax	Lotemax	28	2	2	2	Y	Y	Y	28
	Lotemax	Lotemax	42	.	.	.	Y	Y	Y	28
	Lotemax	Lotemax	90	.	.	.	Y	Y	Y	28
	Lotemax	Lotemax	0	0	0	0	Y	N	Y	7
	Lotemax	Lotemax	1	0	0	0	Y	N	Y	7
	Lotemax	Lotemax	7	0	0	0	Y	N	Y	7
	Lotemax	Lotemax	14	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	28	.	.	.	Y	N	Y	7
(b) (6)	Lotemax	Lotemax	42	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	90	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	0	0	0	0	Y	N	Y	7
	Lotemax	Lotemax	1	0	0	0	Y	N	Y	7
	Lotemax	Lotemax	7	1	1	1	Y	N	Y	7
	Lotemax	Lotemax	14	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	28	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	42	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	90	.	.	.	Y	N	Y	7
	Prednisolone	Lotemax	0	0	0	0	Y	N	Y	7
	Prednisolone	Lotemax	1	0	0	0	Y	N	Y	7
	Prednisolone	Lotemax	7	.	.	.	Y	N	Y	7
	Prednisolone	Lotemax	14	.	.	.	Y	N	Y	7
	Prednisolone	Lotemax	28	.	.	.	Y	N	Y	7
	Prednisolone	Lotemax	42	.	.	.	Y	N	Y	7
	Prednisolone	Lotemax	90	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	0	0	0	0	Y	N	Y	7
	Lotemax	Lotemax	1	0	0	0	Y	N	Y	7
	Lotemax	Lotemax	7	1	0	1	Y	N	Y	7
	Lotemax	Lotemax	14	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	28	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	42	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	90	.	.	.	Y	N	Y	7
	Prednisolone	Prednisolone	0	0	0	0	Y	N	Y	7
	Prednisolone	Prednisolone	1	0	0	0	Y	N	Y	7
	Prednisolone	Prednisolone	7	3	0	3	Y	N	Y	7
	Prednisolone	Prednisolone	14	.	.	.	Y	N	Y	7
	Prednisolone	Prednisolone	28	.	.	.	Y	N	Y	7
	Prednisolone	Prednisolone	42	.	.	.	Y	N	Y	7
	Prednisolone	Prednisolone	90	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	0	0	0	0	Y	N	Y	7
	Lotemax	Lotemax	1	0	0	0	Y	N	Y	7

	Lotemax	Lotemax	7	1	1	1	Y	N	Y	7
	Lotemax	Lotemax	14	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	28	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	42	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	90	.	.	.	Y	N	Y	7
	Prednisolone	Prednisolone	0	0	0	0	Y	N	Y	7
	Prednisolone	Prednisolone	1	0	0	0	Y	N	Y	7
	Prednisolone	Prednisolone	7	2	0	2	Y	N	Y	7
	Prednisolone	Prednisolone	14	.	.	.	Y	N	Y	7
(b) (6)	Prednisolone	Prednisolone	28	.	.	.	Y	N	Y	7
	Prednisolone	Prednisolone	42	.	.	.	Y	N	Y	7
	Prednisolone	Prednisolone	90	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	0	0	0	0	Y	N	Y	7
	Lotemax	Lotemax	1	0	0	0	Y	N	Y	7
	Lotemax	Lotemax	7	2	1	2	Y	N	Y	7
	Lotemax	Lotemax	14	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	28	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	42	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	90	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	0	0	0	0	Y	N	Y	7
	Lotemax	Lotemax	1	1	0	1	Y	N	Y	7
	Lotemax	Lotemax	7	2	0	2	Y	N	Y	7
	Lotemax	Lotemax	14	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	28	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	42	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	90	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	0	0	0	0	Y	N	Y	7
	Lotemax	Lotemax	1	1	0	1	Y	N	Y	7
	Lotemax	Lotemax	7	2	0	2	Y	N	Y	7
	Lotemax	Lotemax	14	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	28	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	42	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	90	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	0	0	0	0	Y	N	Y	7
	Lotemax	Lotemax	1	0	0	0	Y	N	Y	7
	Lotemax	Lotemax	7	1	0	1	Y	N	Y	7
	Lotemax	Lotemax	14	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	28	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	42	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	90	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	0	0	0	0	Y	N	Y	7
	Lotemax	Lotemax	1	0	0	0	Y	N	Y	7

	Lotemax	Lotemax	7	0	0	0	Y	N	Y	7
	Lotemax	Lotemax	14	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	28	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	42	.	.	.	Y	N	Y	7
	Lotemax	Lotemax	90	.	.	.	Y	N	Y	7

Source: Adapted from Listings 16.2.4 of the applicant's study reports. TRT01P: Planned treatment. TRT01A: Actual treatment received. Subjects highlighted in red color are subjects who received a rescue therapy despite having a zero ACI score at all visits prior to receiving a rescue therapy.

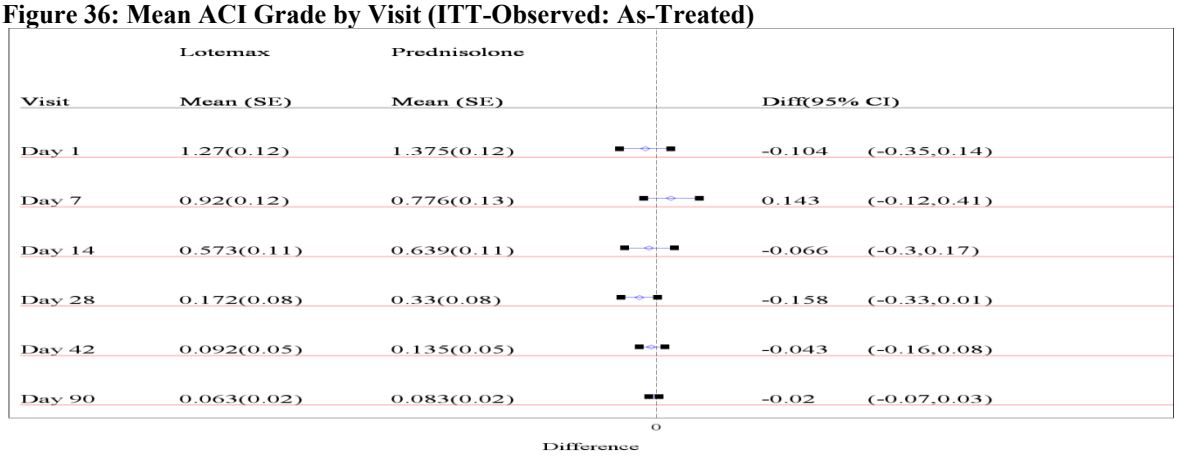
Table 15: Number of Subjects Enrolled by Site (Safety) and Mean (Std) ACI at Day 14 (ITT-OBS)

Site ID	Investigator	Lotemax N=54		Prednisolone N=53	
		# Enrolled (%)	Mean (Std)	# Enrolled (%)	Mean (Std)
110892	Raymond Gerard Areaux, Jr, MD (replaced E.D. Bothun)	3(5.6%)	0.33(0.6)	3(5.7%)	0.67(1.2)
170095	Carlos Gonzales, MD	2(3.7%)	1.5(0.7)	1(1.9%)	0(NA)
170255	Suqin Guo, MD	4(7.4%)	0.67(0.6)	6(11.3%)	0.67(0.5)
170260	Matthew D. Gearinger, MD	2(3.7%)	1(0)	2(3.8%)	0(0)
220248	Phoebe Dean Lenhart, MD	2(3.7%)	0(0)	2(3.8%)	0(0)
250265	Faruk Halim Orge, MD	1(1.9%)	0(NA)	0 (0.0%)	
260249	David A. Plager, MD	5(9.3%)	1.25(1.3)	4(7.5%)	1.75(1)
260871	Alexander Pogrebniak, MD (replaced D. Duss)	2(3.7%)	0.5(0.7)	4(7.5%)	1.75(0.5)
280266	Bibiana Jin-Wan Reiser, MD	30(55.6%)	0(0)	28(52.8%)	0(0)
320875	Federico G. Velez, MD	2(3.7%)	0(.)	1(1.9%)	1(NA)
838313	Nicholas A. Sala, DO	1(1.9%)	1(NA)	2(3.8%)	0.5(0.7)

Source: Reviewer's Analysis

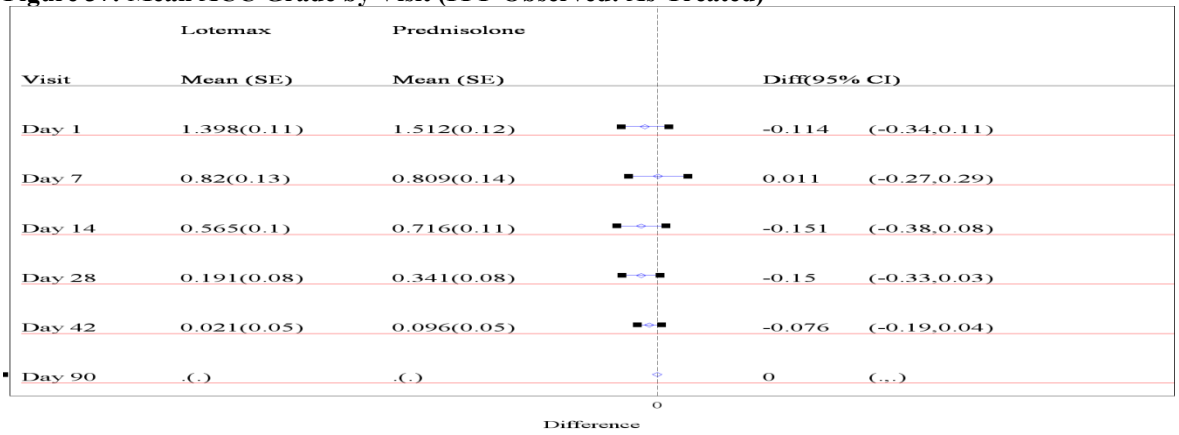
8 Appendix C: Summary of fficacy Analysis Results (As-Treated Analysis)

Figure 36: Mean ACI Grade by Visit (ITT-Observed: As-Treated)



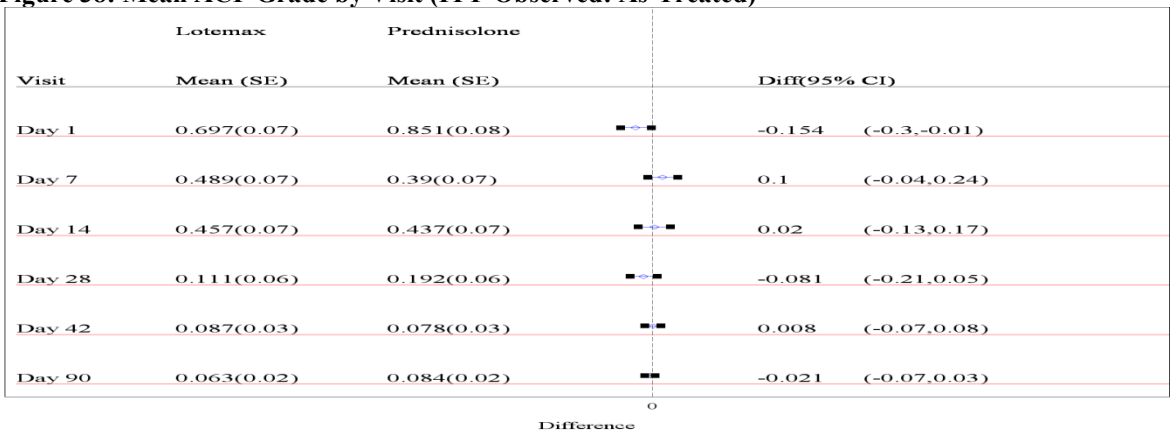
Source: Reviewer's Analysis

Figure 37: Mean ACC Grade by Visit (ITT-Observed: As-Treated)



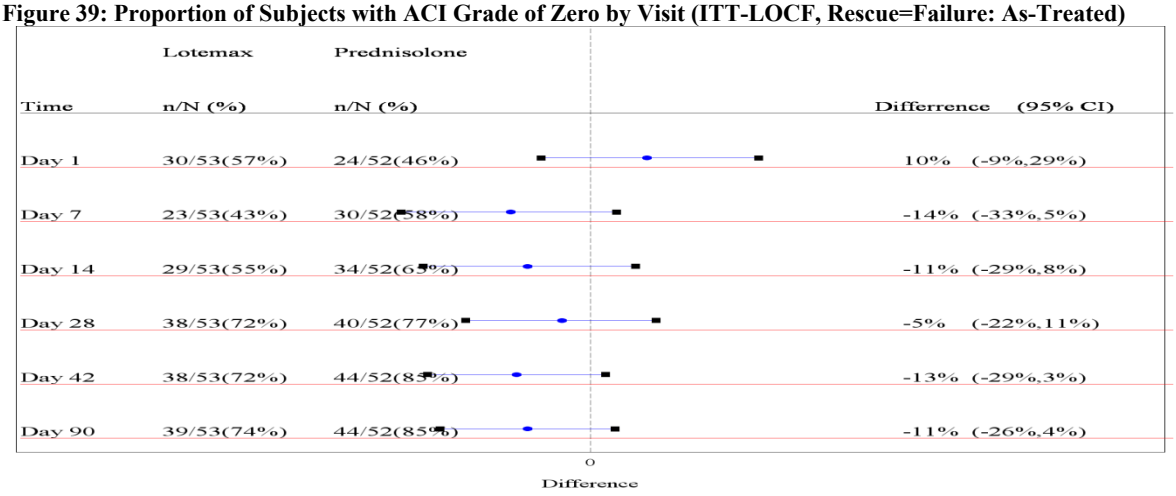
Source: Reviewer's Analysis

Figure 38: Mean ACF Grade by Visit (ITT-Observed: As-Treated)



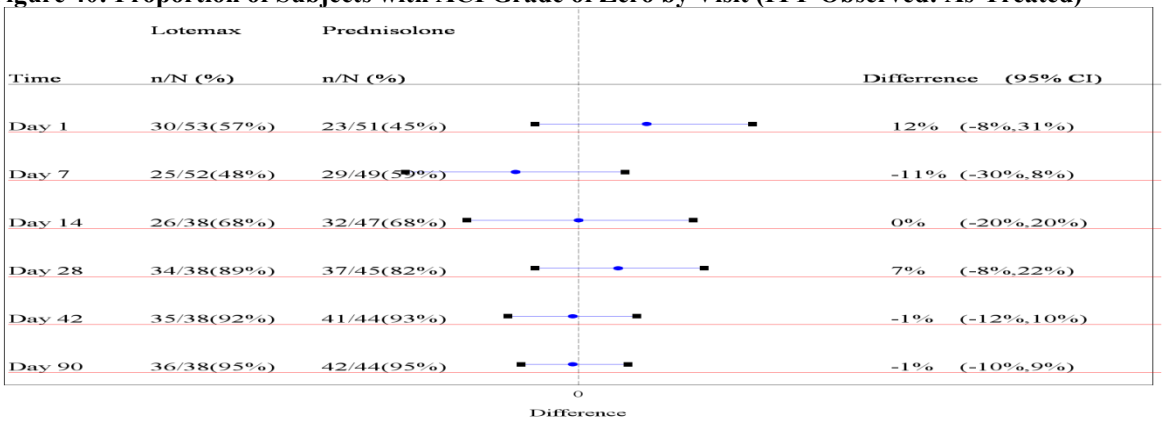
Source: Reviewer's Analysis

Figure 39: Proportion of Subjects with ACI Grade of Zero by Visit (ITT-LOCF, Rescue=Failure: As-Treated)



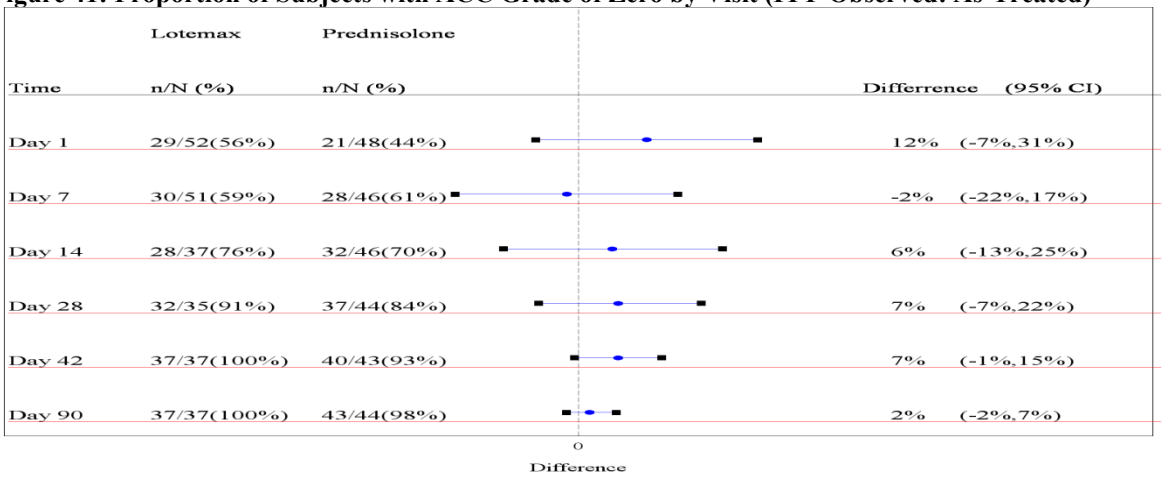
Source: Reviewer's Analysis

Figure 40: Proportion of Subjects with ACI Grade of Zero by Visit (ITT-Observed: As-Treated)



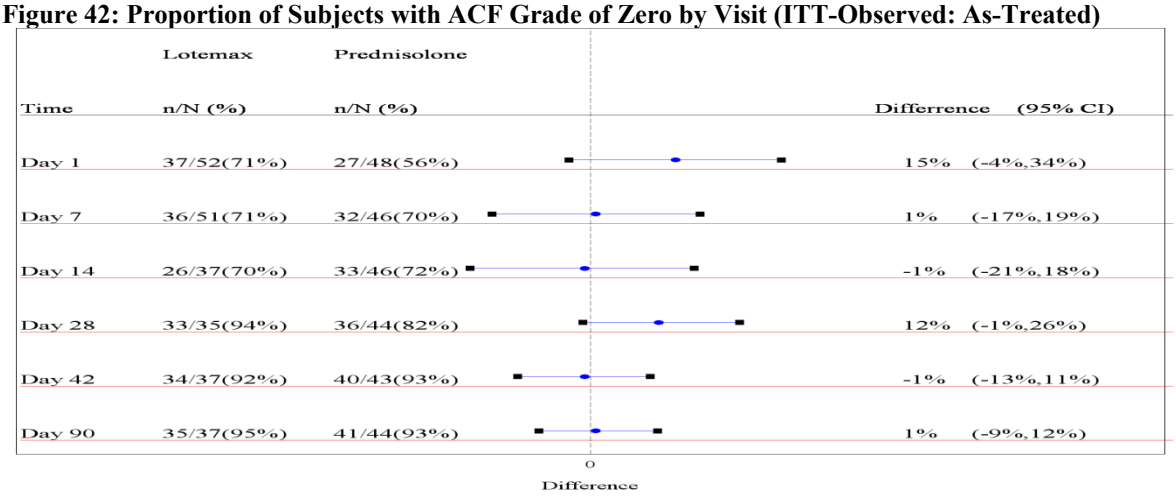
Source: Reviewer's Analysis

Figure 41: Proportion of Subjects with ACC Grade of Zero by Visit (ITT-Observed: As-Treated)



Source: Reviewer's Analysis

Figure 42: Proportion of Subjects with ACF Grade of Zero by Visit (ITT-Observed: As-Treated)



Source: Reviewer's Analysis

9 Appendix D: Cumulative Logistic Regression Model (Sample SAS Code)

```
proc format;
value ccx 0="None"
          1="Mild"
              2="Moderate"
              3="Severe";
              run;
proc freq data=cate;
tables ACI*TRT01P;
where LOCF=0;
format ACI ccx.;
run;
proc logistic data=cate;
class TRT01P / param=ref ref=first;
model ACI = TRT01P / aggregate scale=none;
effectplot interaction (x=TRT01P sliceby=ACI) / polybar;
format ACI ccx.;
where LOCF=0;
run;
```

Cumulative Logit Link

The most popular ordinal link function uses every probability in every function by contrasting the lower levels of Y with the higher levels of Y. Let the *cumulative probability* be denoted as $\theta_{ij} = \Pr(Y_i \leq j)$:

$$\text{logit}(\theta_{i1}) = \log\left(\frac{\pi_{i1}}{\pi_{i2}+\pi_{i3}+\pi_{i4}}\right) \quad \text{logit}(\theta_{i2}) = \log\left(\frac{\pi_{i1}+\pi_{i2}}{\pi_{i3}+\pi_{i4}}\right) \quad \text{logit}(\theta_{i3}) = \log\left(\frac{\pi_{i1}+\pi_{i2}+\pi_{i3}}{\pi_{i4}}\right)$$

This is the *cumulative logit link*. As you move from the first logit function to the second and from the second logit function to the third, the numerator increases and the denominator decreases, so the cumulative logits are increasing.

10 Appendix E: Applicant's summary of Protocol and SAP Amendments

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Changes in the Protocol

The original protocol, dated 05 January 2011, was amended 6 times. A summary of the significant changes is as follows:

Amendment 1, dated 26 May 2011

- Revised the protocol consistent with FDA feedback including increasing the duration of the study and adding a visit, changing the primary efficacy endpoint, specifying that all ophthalmic assessments were to be performed bilaterally at all visits, and increasing the total sample size and number of subjects enrolled by Investigator

Amendment 2, dated 15 November 2011

- Provided clarifications related to dose administration, comparator information, use of standard of care medication, location of study medication storage at the clinical trial sites, test article fill volume and bottle size, obtaining assent from children when applicable, specifying when NSAID use is permitted during the study, recording of concomitant medications for the contralateral non-study eye, specifying the dosage of acetylsalicylic acid allowed for the breastfeeding mother/wet nurse
- Clarified that the ITT set was to be used for the secondary efficacy analyses, and that the PP set was to be used for the primary efficacy analysis

Amendment 3, dated 15 December 2011

- Provided clarifications related to comparator information, and the provision of all investigational products by the Sponsor

The final SAP, version 1.0 (dated 04 June 2012) was amended once, primarily to reflect changes based on protocol amendment 6. A summary of the other significant changes in version 2.0 (dated 12 May 2017) is as follows:

- Clarified that the ACI grade was determined using either slit lamp biomicroscopy or a penlight with handheld magnification, and that the grading from each method was to be combined into one ACI grade to be used as the primary endpoint.
- Clarified that the latest version of SAS (version 9.4) would be used for statistical analyses
- Deleted reference to secondary analyses using an ANCOVA model
- Clarified that secondary analyses of proportion of subjects with presence/absence and total area, if present, of synechia at each visit and of proportion of subjects with presence/absence and total number, if present, of precipitates on t he implant and cornea at each visit would be conducted on the study eye only
- Clarified that summaries of adverse events would refer to treatment-emergent adverse events.

Amendment 4, dated 27 March 2012

- Revised the protocol consistent with FDA feedback including changing total enrollment, modifying the description of the primary efficacy endpoint, changing the visit on which the primary efficacy endpoint was to be analyzed, changing the description of the secondary efficacy endpoints, changing the sample size calculation, changing the hypotheses to align with the recalculation of the confidence interval, changing the description of the primary and secondary analysis, changing the visits on which the secondary efficacy endpoints were to be analyzed, changing the Anterior Chamber Inflammation grading scale, clarified description of ITT data set, clarified handling of missing data

Amendment 5, dated 04 June 2012

- Provided clarifications to reflect the data sets to be used for secondary efficacy analyses, variables to be used for subgroups analyses, and the description of the tolerability endpoints

Amendment 6, dated 22 May 2013

- Revised the protocol in accordance with FDA's Written Request by updating the sample size, changing study duration and visit windows, changing primary and secondary efficacy endpoint, changing the hypotheses to align with the revised non-inferiority margin
- Revised the population on which the power calculation was based
- Clarified the MedDRA dictionary version to be used for coding AEs

The original protocol and six amendments, including their summary of changes, are provided in Appendix 16.1.1.

9.8.2 Changes in the Statistical Analysis Plan

The final SAP, version 1.0 (dated 04 June 2012) was amended once, primarily to reflect changes based on protocol amendment 6. A summary of the other significant changes in version 2.0 (dated 12 May 2017) is as follows:

- Clarified that the ACI grade was determined using either slit lamp biomicroscopy or a penlight with handheld magnification, and that the grading from each method was to be combined into one ACI grade to be used as the primary endpoint.
- Clarified that the latest version of SAS (version 9.4) would be used for statistical analyses
- Deleted reference to secondary analyses using an ANCOVA model
- Clarified that secondary analyses of proportion of subjects with presence/absence and total area, if present, of synechia at each visit and of proportion of subjects with presence/absence and total number, if present, of precipitates on the implant and cornea at each visit would be conducted on the study eye only
- Clarified that summaries of adverse events would refer to treatment-emergent adverse events.

11 Appendix F: ACC, ACF and ACI (measured using penlight) Grade Description

Anterior Chamber Cells (for those subjects that can be examined with a slit lamp): Assess accumulation of white blood cells in aqueous. Pigment cells and red blood cells are to be ignored. Assess anterior chamber using a high power field slit beam of 1 mm x 1 mm.

0 = No cells seen

1 = 1 - 5 cells

2 = 6 - 15 cells

3 = 16 - 30 cells

4 = >30 cells

Anterior Chamber Flare (for those subjects that can be examined with a slit lamp): Assess scattering of a slit lamp light beam when directed into the anterior chamber (Tyndall effect).

0 = None	No Tyndall effect
1 = Mild	Tyndall effect barely discernible
2 = Moderate	Tyndall effect in anterior chamber is moderately intense. Iris pattern is seen clearly
3 = Severe	Tyndall effect in anterior chamber is severely intense. Iris pattern cannot be seen clearly
4 = Very severe	Tyndall effect is very severely intense. The aqueous has a white and milky appearance

Anterior Chamber Inflammation (for subjects that can only be examined with a pen light and a 20 dpt magnifying lens):

0 = None	Clear anterior chamber with no visible clouding (Tyndall effect and cells combined). Red reflex normal
1 = Mild	Mild anterior chamber clouding. Clear iris pattern on visualization. Red reflex normal
2 = Moderate	Moderate anterior chamber clouding
3 = Severe	Severe anterior chamber clouding. Iris pattern not clearly visualized. Red reflex diminished
4 = Very severe	Severe anterior chamber clouding with a white and/or milky appearance of the anterior chamber. Red reflex absent or severely diminished

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ABEL T ESHETE
05/23/2018

YAN WANG
05/23/2018
I concur.