CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA208219
Related IND#	IND102654
Drug Name:	LOTEMAX SM (Loteprednol etabonate ophthalmic gel, 0.38%)
Indication(s):	Treatment of postoperative pain and inflammation following ocular surgery
Applicant:	Bausch & Lomb Inc.
Date(s):	Stamp date: April 25, 2018
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Review Priority:	Standard
Biometrics Division:	DBIV
Statistical Reviewer:	Abel Eshete, PhD, Statistical Reviewer
Concurring Reviewers:	Yan Wang, PhD, Statistical Team Leader
Medical Division:	Division of Transplant and Ophthalmology Products (DTOP)
Clinical Team:	Martin Nevitt, MD, Medical Officer
	William Boyd, MD, Medical Team Leader
Project Manager:	Wendy Streight, PhD, Regulatory Health Project Manager

Keywords: Pain, Inflammation, Loteprednol etabonate, Ocular surgery.

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1 EXECUTIVE SUMMARY

Bausch and Lomb Inc. submitted this NDA application seeking approval of Lotemax SM™ (Loteprednol etabonate ophthalmic gel, 0.38%) dosed one-drop three times daily (TID), for the indication of resolution of pain and inflammation following ocular surgery. The Applicant submitted the results of two pivotal studies (Study 842 and Study 875) to support this indication. The main objective of this review was to evaluate whether the efficacy results in these two studies support the proposed indication.

The two pivotal studies were randomized, multicenter, double-masked, parallel-group, vehicle-controlled studies. Each study randomized subjects in 1:1:1 ratio to Vehicle and two active control arms [Lotemax SM taken twice daily (BID), and Lotemax SM taken three times daily (TID)]. All subjects enrolled in these studies were from US sites (514 subjects in Study 842 and 600 subjects in Study 875) and undergone cataract extraction with intraocular lens implantation. The total duration of each study was approximately 4 weeks. Efficacy and safety assessments were conducted at post cataract surgery Days 1, 3, 8, 15, and 18. Anterior chamber inflammation quantified by investigators using a 5-point scale (0=No cells, 1=1-5 cells, 2=6-15 cells, 3=16-30 cells, 4=>=30 cells) and ocular pain assessed by the patient and recorded by investigators using a 6-point scale (0=None, 1=Minimal, 2=Mild, 3=Moderate, 4=Moderately Severe, 5=Severe) were the two main efficacy outcomes of interest. The studies had two primary efficacy endpoints both assessed at post-surgery Day 8: the proportion of subjects with complete resolution of anterior chamber cell inflammation (cell score=0) and the proportion of subjects with complete resolution of ocular pain (pain score=0).

The primary efficacy analysis compared the TID and BID administrations of Lotemax SM against Vehicle using a Pearson's chi-square test. The primary efficacy analysis was conducted based on all randomized subjects (ITT population) with missing data imputed as treatment failure. Subjects who received rescue therapy prior to the evaluation of the primary efficacy endpoints were also considered treatment failures. The primary efficacy results from the two studies provided evidence supporting the efficacy of the Lotemax SM TID for the treatment of ocular inflammation and pain following cataract surgery (Table 1). The treatment difference (TID-Vehicle) in the proportion of subjects with complete resolution of anterior chamber inflammation at post-operative Day 8 was 19.4% (95% CI: 11.3%, 27.4%) in Study 842 and 10.4% (95% CI: 1.9%, 18.9%) in Study 875. Similarly, the differences (TID-Vehicle) in the proportion of subjects with complete resolution of ocular pain at post-operative Day 8 were 25.4% (95% CI: 15.4%, 35.4%) and 25.8% (95% CI: 16.6, 34.9%) in Study 842 and Study 875, respectively. Besides, in both studies, a higher proportion of subjects in the Vehicle arm received rescue therapy compared to subjects in the two Lotemax SM arms (Table 2).

Study 842 also provided statistically significant difference between Lotemax SM BID and Vehicle with respect to both primary efficacy endpoints. In Study 875 however, there was no statistically significant difference between Lotemax SM BID and Vehicle in the proportion of subjects with complete resolution of anterior chamber cells at Day 8. Consequently, because of the pre-specified hierarchical testing procedure, no formal statistical conclusion of efficacy could be made for Lotemax SM BID with respect to the pain outcome in this study (Table 1).

The safety results showed that a higher incidence of ocular adverse events (AE) was reported in the Vehicle arm compared to the two Lotemax SM arms. The most frequently reported AEs among subjects who received the two Lotemax SM arms were photophobia, eye pain, and vitreous floater. No deaths were reported, and only one subject in the Lotemax SM BID arm reported serious AE compared to 3 subjects in the Vehicle arm.

In conclusion, the primary efficacy results as well as supportive analyses of secondary efficacy endpoints, provide evidence supporting the efficacy of the TID administration of Lotemax SM for the treatment of ocular inflammation and pain following cataract surgery.

Table 1: Applicant's Primary Efficacy Analysis (ITT)

	Treatments			**% Diff (95% CI)**	
Outcome	**Vehicle N=172**	**BID N=171**	**TID N=171**	**BID- Vehicle**	**TID- Vehicle**
	Study 842				
ACC; n (%)	16 (9.3)	46 (26.9)	49 (28.7)	17.6 (9.7, 25.5)	19.4 (11.3, 27.4)
Pain: n (%)	82 (47.7)	126 (73.7)	125 (73.1)	26.0 (16.0, 36.0)	25.4 (15.4, 35.4)
	Study 875				
Outcome	**Vehicle N=199**	**BID N=201**	**TID N=200**	**BID- Vehicle**	**TID- Vehicle**
ACC; n (%)	40 (20.1)	52 (25.9)	61 (30.5)	5.8 (-3.6, 15.2)	10.4 (1.9, 18.9)
Pain: n (%)	99 (49.7)	151 (75.1)	151 (75.5)	25.4 (14.9, 35.9)	25.8 (16.6, 34.9)

Source: Table 6 of the Applicant's study reports. n=number of subjects with complete resolution; ACC: Anterior chamber cells; Pain: Ocular pain

Table 2: Summary of Subjects Who Received Rescue Medication on or Prior to a given Visit

	Study 842			**Study 875**		
Visits	**Vehicle N=172**	**BID N=171**	**TID N=171**	**Vehicle N=199**	**BID N=201**	**TID N=200**
Day 3	40 (23.2)	10 (5.8)	14 (8.2)	33 (16.6)	4 (2.0)	9 (4.5)
Day 8	72 (41.9)	24 (14.0)	19 (11.1)	62 (31.2)	23 (11.4)	20 (10.0)
Day 15	88 (51.2)	36 (21.1)	31 (18.1)	71 (35.7)	49 (24.4)	33 (16.5)
Day 18	88 (51.2)	36 (21.1)	31 (18.1)	71 (35.7)	49 (24.4)	33 (16.5)

Source: Reviewer's Analysis.

Reviewer's remark: For study 875, the Applicant used a Bonferroni-based tree structured gatekeeping strategy to control the overall Type-I error rate at 5%. In this approach, the test for the treatment differences was conducted hierarchically at 2.5% level. The Applicant however provided a 95% confidence interval for treatment differences. To align the confidence interval with the levels of significance used for the test of treatment difference, this reviewer provided a 97.5% confidence interval for the treatment differences in this study. The conclusion of efficacy remains unchanged.

Table 3: Reviewer's Primary Efficacy Analysis Study 875 (ITT)

	Treatments			**% Diff (97.5% CI)[1]**	
Outcome	**Vehicle N=172**	**BID N=171**	**TID N=171**	**BID- Vehicle**	**TID- Vehicle**
ACC; n (%)	40 (20.1)	52 (25.9)	61 (30.5)	5.8 (-3.6, 15.2)	10.4 (0.7, 20.1)
Pain: n (%)	99 (49.7)	151 (75.1)	151 (75.5)	25.4 (14.9, 35.9)	25.8 (15.3, 36.2)

Source: Reviewer's Analysis. ACC: Anterior chamber cells; Pain: Ocular pain. [1]Per the gatekeeping strategy, a 97.5% CI is provided

2 INTRODUCTION

This NDA included data from two pivotal Phase 3 studies (842 and 875) to support the safety and efficacy of Lotemax SM dosed one-drop three times daily (TID) for the treatment of post-operative inflammation and pain following ocular surgery. A third study, Study 843, is also included in the submission but was only used to support the safety evaluation of Lotemax SM.

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

Lotemax SM is a corticosteroid developed for the treatment of post-surgical pain and inflammation in subjects who have undergone cataract extraction with intraocular lens implantation. Lotemax SM contains an active ingredient that was used in three other approved products developed for the same indication by the same applicant: Loteprednol etabonate 0.5% ophthalmic suspension (NDA 20583), Loteprednol etabonate 0.5% ointment (NDA 200738), and Loteprednol etabonate 0.5% gel (NDA 202872).

Reviewer's remark: The Applicant stated that the smaller particle size in loteprednol etabonate ophthalmic gel, 0.38% (LE gel 0.38%) serves to increase ocular penetration and residence time in anterior segment tissues while retaining many of the advantages of the current LE gel, 0.5% formulation. Per the Applicant, the results of their pharmacokinetic study conducted in pigmented rabbits revealed that the lower dose (0.38%) provides significantly greater exposure to LE in aqueous humor and similar or greater exposure in cornea and iris/ciliary body, compared with the current 0.5% Lotemax gel.

2.1.2 History of Drug Development

The product development of Lotemax SM was conducted under IND 102654. The applicant had an End-of-Phase 2 and pre-NDA meetings with the Agency. The End-of-Phase 2 meeting was held on June 13, 2013. The meeting package included protocol synopses for Studies 842 and 843. After the review of the synopses, the Agency found the proposed design of the two studies acceptable. The statistical team found the proposed method to deal with missing data, which treats all subjects with missing efficacy outcomes and subjects who receive rescue therapy as treatment failures, acceptable. The statistical review team stated that the proposed sensitivity analyses appears acceptable provided the impending missing data is small and is balanced between treatment arms. The review team however stated that, if the impending missing data is large, additional sensitivity analyses using multiple imputation approach should be conducted to further evaluate the impact of missing data.

The Applicant had the pre-NDA meeting with the Agency on January 30, 2018. During this meeting, the Applicant presented the results of three Phase 3 studies (Studies 842, 843 and 875).

Per the Applicant, the objective of the first Phase 3 study (842) was to evaluate the safety and efficacy of LE gel,0.38% dosed both TID and BID. The second study (843) was a 2-arm study designed to evaluate the efficacy of LE gel,0.38% dosed BID only. Per the Applicant, after review of the results of study 843, in which there was not statistical differentiation between Vehicle and BID treatment, they decided to conduct Study 875 to further evaluate the BID and TID dosing regimens.

2.1.3 Studies Reviewed

This NDA review was conducted mainly based on data from two Phase 3, prospective, multicenter, randomized, parallel-arm, double-masked, vehicle-controlled studies (Study 842 and Study 875). Study 842 and Study 875 enrolled 514 and 600 subjects, respectively. All study sites are in the United States (US). Brief summaries of the two pivotal studies, as provided by the Applicant, are presented in Table 4. A summary of a Phase 3 study (Study 483) considered as part of the safety evaluation is presented in the Appendix.

Table 4: Summary of Studies (842 and 875)

Trial ID	Design*	Treatment/Sample size	Endpoint/Analysis	Applicant's finding
Study Name: Study 842 Primary Objective: The primary objective was to evaluate the safety and efficacy of loteprednol etabonate (LE) ophthalmic gel, 0.38% (twice per day [BID] and 3 times per day [TID]) for the treatment of postoperative inflammation and pain following cataract surgery.	MC, R, DB, VC PG	-Vehicle (N=172) -LE gel 0.38% BID (N=171) -LE gel 0.38% TID (N=171)	Primary Endpoints: 1) The proportion of subjects with complete resolution of AC cells (cell score = 0) in the study eye at Visit 5 (Postoperative Day 8) for LE gel 0.38% and vehicle 2) The proportion of subjects with Grade 0 pain in the study eye at Visit 5 (Postoperative Day 8) for LE gel 0.38% and vehicle The primary efficacy analysis was based on the ITT population with missing data imputed as treatment failures (subjects placed on rescue medication prior to the visit being summarized were also considered failures).	Statistically significant greater proportions of ITT subjects in both the LE gel 0.38% BID and LE gel 0.38% TID treatment groups compared to the vehicle treatment group had complete resolution of AC cells (26.9% [46/171] and 28.7% [49/171] compared to 9.3% [16/172]) and complete resolution of ocular pain (73.7% [126/171] and 73.1% [125/171] versus 47.7% [82/172]) at Visit 5. For each primary endpoint, there was a statistically significant difference between each active treatment group (i.e., LE gel 0.38% BID and LE gel 0.38% TID) and vehicle group (Pearson Chi-squared tests: $p < 0.0001$) with the prospectively defined analysis population (i.e., ITT population with missing data imputed as treatment failures). The results of sequential testing of the primary endpoints thereby demonstrated success for resolution of inflammation and treatment of pain for both BID and TID dosing.
Study Name: Study 875 Primary Objective: The primary objective was to evaluate the safety and efficacy of loteprednol etabonate (LE) ophthalmic gel,	MC, R, DB, VC PG	-Vehicle (N=199) -LE gel 0.38% BID (N=201) -LE gel 0.38% TID (N=200)	Primary Endpoints: 1) The proportion of subjects with complete resolution of AC cells (cell score = 0) in the study eye at Visit 5 (Postoperative Day 8) for LE gel 0.38% and vehicle	Significantly greater proportions of subjects in the LE gel 0.38% TID group (30.5%), but not the LE gel 0.38% BID group (25.9%), compared to the vehicle group (20.1%) had complete resolution of AC cells in the study eye in the primary efficacy population (ITT population with missing values and post-rescue values imputed as treatment failures).

0.38% (twice per day [BID] and 3 times per day [TID]) for the treatment of postoperative inflammation and pain following cataract surgery.			2) The proportion of subjects with Grade 0 pain in the study eye at Visit 5 (Postoperative Day 8) for LE gel 0.38% and vehicle The primary efficacy analysis was based on the ITT population with missing data imputed as treatment failures (subjects placed on rescue medication prior to the visit being summarized were also considered failures).	In addition, a significantly greater proportion of subjects in the LE gel 0.38% TID group compared to vehicle (75.5% versus 49.7%) had complete resolution of ocular pain in the study eye at Visit 5. As no statistically significant difference was observed in complete resolution of AC cells with LE gel 0.38% BID versus vehicle (Family 1 hypothesis), the complete resolution of ocular pain (Family 2 hypothesis) with BID dosing was not eligible to claim success under the Bonferroni gatekeeping strategy. Thus, statistical superiority was met with LE gel 0.38% TID versus vehicle, but not for LE gel 0.38% BID versus vehicle in the resolution of AC cells and ocular pain.

Source: Applicant's submitted study reports.

2.2 Data Sources

The data sources for this review included the applicant's clinical study reports for all studies and the integrated safety and efficacy analysis reports. Additionally, the applicant submitted SAS datasets both as SDTM and ADAM data formats electronically. The data sets used in this review are located at: \\Cdsesub1\evsprod\NDA208219\0001\m5\datasets\. The pain and inflammation outcomes at screening and subsequent measurement times were included in the "adeff.xpt" dataset. An indicator variable (PARAMCD) was included to distinguish the different outcomes (pain, inflammation, flare).

For the primary efficacy analysis of the pain and inflammation outcomes, the variable CRIT2FL is used. This variable takes a value of "Y" if the score was zero, or "N" if the score was greater than zero or the subject received a rescue therapy prior to Day 8 or has missing data at Day 8. The treatment variable, given both as numeric (TRT01P) and character (TRT01PN), was also included in the above dataset. The adverse events and treatment exposures were included in the "adae.xpt" dataset.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data were generally of decent quality. The final statistical analysis plan and the amended protocols were all submitted. The reviewer replicated the Applicant's primary and secondary efficacy analyses.

3.2 Evaluation of Efficacy

This section summarizes the design of the two pivotal studies and the corresponding efficacy results submitted by the Applicant and observed in the reviewer's analyses.

3.2.1 Study Design and Endpoints

The two pivotal studies were randomized, multicenter, double-masked, parallel-group, vehicle-controlled studies. Each study randomized subjects in 1:1:1 ratio into Vehicle and two active control arms [Lotemax taken twice daily (BID), and Lotemax taken three times daily (TID)]. The total duration of each study was approximately 4 weeks. Efficacy and safety assessments were conducted at post-operative Days 1, 3, 8, 15, and 18. Anterior chamber inflammation quantified by investigators using a 5-point scale (0=No cells, 1=1-5 cells, 2=6-15 cells, 3=16-30 cells, 4=>=30 cells) and ocular pain assessed by the patient and recorded by investigators using a 6-point scale (0=None, 1=Minimal, 2=Mild, 3=Moderate, 4=Moderately Severe, 5=Severe) were the two efficacy outcomes of interest. The studies have two primary efficacy endpoints both assessed at post-surgery Day 8: the proportion of subjects with complete resolution of anterior chamber cell inflammation (cell score=0) and the proportion of subjects with complete resolution of ocular pain (pain zero=0).

According to the study protocols, investigators had the discretion to prescribe rescue medication for subjects with worsening or no change in the grade of inflammation in the study eye compared with the previous visit at postoperative Days 3, 8, 15, and 18. Subjects requiring rescue medication for inflammation were to stop treatment with the study drug and were to be promptly discontinued from the study. Subjects who received rescue medication were counted as treatment failures as of the date of receiving rescue medication.

3.2.2 Statistical Methods

3.2.2.1 Analysis Populations

The following analysis populations were defined in the two studies for the evaluation of efficacy and safety:

- Intent to Treat (ITT): The ITT population includes all randomized subjects. The ITT population will be used for the analyses of all efficacy endpoints.

- Per Protocol (PP): The PP population includes all ITT subjects who remain in study through postoperative Day 8 and who have not deviated from the protocol in any way likely to seriously affect the primary outcome of the study.

- Safety: The safety population includes all subjects who received at least 1 dose of study drug.

3.2.2.2 Analysis Method

The protocol defined primary efficacy analysis compared the efficacy of the two doses of Lotemax SM against Vehicle using a Pearson chi-square. A 95% asymptotic confidence interval around treatment differences was also provided. The two studies however used slightly different approaches to control the overall Type-I error rate at 5%. Study 842 used a hierarchical testing

procedure which first tested the difference between Lotemax SM TID and Vehicle in the proportion of subjects with complete resolution of anterior chamber cells at Day 8. This test was followed by the comparison of the same dose in the proportion of subjects with complete resolution of pain at Day 8. The Lotemax SM BID was then compared with Vehicle with respect to the two endpoints in the same order. Each subsequent test was conducted only if the previous test was statistically significant at 5% level of significance. Study 875 used a Bonferroni-based tree structured gatekeeping strategy. In this approach, the TID and BID doses of Lotemax SM were simultaneously compared against Vehicle at 2.5% level of significance with respect to the proportion of subjects with complete resolution of anterior chamber cells at Day 8. The comparison of each Lotemax SM dose against Vehicle for the proportion of subjects with complete resolution of pain at Day 8 was then conducted at 2.5% level of significance only if the corresponding test for the anterior chamber cells outcome was statistically significant at 2.5% level.

The primary efficacy analyses in both studies were conducted based on the ITT population. Subjects with missing efficacy outcomes for the primary efficacy endpoints and subjects who received rescue therapy prior to the evaluation of the primary efficacy endpoints were treated as treatment failures (score of >0) in the primary efficacy analyses. Supportive analyses of the primary endpoints were conducted on the per-protocol (PP) population with observed data only, and on the ITT population with all missing data (including data after rescue use) imputed using the last observation carried forward (LOCF) approach. The reviewer conducted a tipping point analysis to determine the number of Vehicle treated subjects who received a rescue therapy (and hence set as treatment failures) that need to be set as treatment successes for the treatment difference to no longer be statistically significant.

Note that, the main interest in this NDA was to evaluate the efficacy of the drug in achieving complete clearance of pain and inflammation. The efficacy outcomes of interest however are ordinal in nature. The reviewer thus used a proportional odds logistic regression model to compare the Lotemax SM TID and Vehicle arms with respect to odds of having higher anterior chamber cells scores versus lower scores. The logistic model included the ordinal anterior chamber cells scores (0, 1, 2, 3 and 4) as dependent variables and treatment as the only covariate. The same analysis is also conducted for the pain outcome. In these analyses, the inflammation and pain scores for subjects who received rescue therapy and those with missing data at Day 8 were set to 4 (>=30 cells) and 5 (Severe), respectively.

To provide an estimate of a risk-benefit profile of the drug, this reviewer conducted a risk-benefit analysis at the subject level. This analysis first identified the risk-benefit outcome (four possible scenarios) for each individual subject and then calculated the proportion of subjects in each scenario for each treatment arm. The first scenario, referred to here as the best-case scenario is the case in which an anterior chamber cells score of zero at Day 8 was observed without incurring any ocular adverse event (AE) during the study. The worst-case scenario is incurring an ocular AE during the study without achieving a zero anterior chamber cells score at Day 8. The other two scenarios are having no anterior chamber cells at Day 8 (benefit) with ocular AE, and no benefit and no ocular AE.

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

3.2.3.1 Demographic and Baseline Characteristics

There were no noticeable baseline imbalances between the two Lotemax SM arms and the Vehicle arm in the demographics of age, gender, race or iris color. In both studies, more female participants than male participants were enrolled; and most of the study participants were white (Table 5).

Table 5: Baseline and Demographic Characteristics (ITT)

	Study 842			Study 875		
	Vehicle N=172	**BID N=171**	**TID N=171**	**Vehicle N=199**	**BID N=201**	**TID N=200**
Age (years)						
Mean (SD)	69.0 (8.56)	70 (8.34)	70.5 (8.15)	68.5 (8.92)	68.3 (9.11)	67.9 (9.32)
Median	70	70	71	68	69.0	69.0
Min, Max	42, 87	46, 96	43, 89	38, 88	42, 91	36, 92
Gender, n (%)						
Male	72 (41.9)	77 (45.0)	82 (48.0)	83 (41.7)	84 (41.8)	70 (35.0)
Female	100 (58.1)	94 (55.0)	89 (52.0)	116 (58.3)	117 (58.2)	130 (65.0)
Race, n (%)						
American Indian or Alaskan	0	0	1 (0.6)	0	1 (0.5)	1 (0.5)
Asian	23 (13.4)	18 (10.5)	18 (10.5)	7 (3.5)	13 (6.5)	9 (4.5)
Black or African American	24 (14.0)	22 (12.9)	22 (12.9)	14 (7.0)	23 (11.4)	23 (11.5)
Native Hawaiian or Other Pacific	2 (1.2)	0	1 (0.6)	0	1 (0.5)	0
White	119 (69.2)	126 (73.7)	125 (73.1)	169 (84.9)	158 (78.6)	163 (81.5)
Other	3 (1.7)	4 (2.3)	3 (1.8)	9 (4.5)	4 (2.0)	3 (1.5)
Multiple Races Checked	1 (0.6)	1 (0.6)	1 (0.6)	0	1 (0.5)	1 (0.5)
Iris Color – Study Eye, n (%)						
Blue	35 (20.3)	39 (22.8)	35 (20.5)	47 (23.4)	47 (23.4)	49 (24.5)
Brown	106 (61.6)	100 (58.5)	102 (59.6)	115 (57.2)	115 (57.2)	112 (56.0)
Green	11 (6.4)	8 (4.7)	10 (5.8)	9 (4.5)	9 (4.5)	5 (2.5)
Hazel	20 (11.6)	23 (13.5)	23 (13.5)	28 (13.9)	28 (13.9)	32 (16.0)
Other	0	1 (0.6)	1 (0.6)	2 (1.0)	2 (1.0)	2 (1.0)

Source: Table 5 of the applicant's study reports

3.2.3.2 Subject Disposition

The summary of the patient disposition is presented in Table 6. In both studies, higher proportion of subjects in the Vehicle arm discontinued the study. The main reason for study discontinuation was rescue use.

Table 6: Subject Disposition (ITT: All Randomized)

	Study 842			Study 875		
Categories, n (%)	**Vehicle N=172**	**BID N=171**	**TID N=171**	**Vehicle N=199**	**BID N=201**	**TID N=200**
Treated	172	171	170[a]	198	201	200[b]
Completed the Study [c]	80 (46.5)	133 (77.8)	139 (81.3)	122 (61.3)	145 (72.1)	159 (79.5)
Discontinued the Study	92 (53.5)	38 (22.2)	32 (18.7)	77 (38.7)	56 (27.9)	41 (20.5)
Reason for Study Discontinuation						
Lack of Efficacy	0	0	0	0	0	0
Adverse Event(s)	2 (1.2)	1 (0.6)	0	1 (0.5)	1 (0.5)	2 (1.0)
Rescue Therapy Use	88 (51.2)	36 (21.1)	31 (18.1)	71 (35.7)	49 (24.4)	33 (16.5)
Protocol Violation(s)	0	0	0	0	0 (0.0)	0
Lost to Follow-Up	1 (0.6)	1 (0.6)	0	1 (0.5)	5 (2.5)	5 (2.5)

Investigator Decision	1 (0.6)	0	0	1 (0.5)	0	0
Other	0	0	1 (0.6)	3 (1.5)	1 (0.5)	1 (0.5)

Source: Table 4 of Applicant's submitted Study Reports. [a] one subject randomized to Lotemax SM (TID) arm was withdrawn before treatment. [b]one subject randomized to Lotemax SM (TID) arm received BID (This subject is included in the TID arm for efficacy analysis (ITT) but was included in the BID arm for safety analysis). [b] one subject randomized to Lotemax SM (BID) arm was withdrawn before treatment. ITT: all randomized subjects. Safety: Subjects who received at least one dose of study drug. [c] Completed study through Day 18.

The number of subjects included in the different analysis sets is summarized in Table 7. The summary of subjects who are listed as having clinically significant protocol deviations and hence were discontinued from the per-protocol population is presented in Table 8. A total of 64 and 62 subjects were listed as having clinically significant protocol deviations in Studies 842 and 875, respectively. The most commonly observed protocol deviations were inclusion/exclusion criteria not met and use of exclusionary/prohibited medication (Table 8). In addition to subjects with clinically significant protocol deviations listed in Table 8, subjects who were not in the study through Day 8 were also excluded from the per-protocol population.

Table 7: Analysis Sets

	Study 842			**Study 875**		
Analysis set	**Vehicle N=172**	**BID N=171**	**TID N=171**	**Vehicle N=199**	**BID N=201**	**TID N=200**
ITT	172 (100)	171(100)	171 (100)	199 (100)	201 (100)	200 (100)
Per-protocol	113 (65.7)	133 (77.8)	141 (82.5)	139 (69.8)	181 (90.0)	168 (84.0)
Safety	172 (100)	171(100)	170 (99.4) [a]	198 (99.5)	202 (100) [b]	199 (99.5)

Source: Table 4 of the applicant's study report. [a] one subject randomized to Lotemax SM (TID) arm was withdrawn before receiving treatment. [b]one subject randomized to Lotemax SM (TID) arm received BID. This subject is included in the TID arm for efficacy analysis (ITT) but was included in the BID arm for safety analysis.

Table 8: Summary of Significant Protocol Deviations (ITT)

	Study 842			**Study 875**		
Deviations, n (%)	**Vehicle N=172**	**BID N=171**	**TID N=171**	**Vehicle N=199**	**BID N=201**	**TID N=200**
Did not meet Inclusion/Exclusion criteria	2 (1.2)	6 (3.5)	3 (1.8)	12 (6.0)	5 (2.5)	13 (6.5)
Visit/Procedure Not Done	1 (0.6)	3 (1.8)	2 (1.2)	3 (1.5)	2 (1.0)	0 (0.0)
Out-of-window Visit	7 (4.1)	4 (2.3)	4 (2.4)	1 (0.5)	0 (0.0)	0 (0.0)
Non-compliance with IP Dosing	4 (2.3)	2 (1.2)	3 (1.8)	1 (0.5)	1 (0.5)	1 (0.5)
Incorrect IP Treatment Assignment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Incorrect IP Dosing Regimen	1 (0.6)	2 (1.2)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Exclusionary/prohibited medication	5 (2.9)	1 (0.6)	1 (0.6)	9 (4.5)	6 (3.0)	7 (3.5)
Other	3 (1.7)	5 (2.9)	4 (2.4)	0 (0.0)	1 (0.5)	0 (0.0)

Source: Adapted from Table 14.1.2 of the Study reports

The summary of subjects who received rescue therapy on or prior to a given visit is presented in Table 9. In both studies, a higher proportion of subjects in the Vehicle arm received rescue therapy compared to the two Lotemax SM dosing regimens.

Table 9: Cumulative Summary of subjects who Received Rescue Therapy

	Study 842			**Study 875**		
Visit	**Vehicle N=172**	**BID N=171**	**TID N=171**	**Vehicle N=199**	**BID N=201**	**TID N=200**
Day 3	40 (23.2)	10 (5.8)	14 (8.2)	33 (16.6)	4 (2.0)	9 (4.5)
Day 8	72 (41.9)	24 (14.0)	19 (11.1)	62 (31.2)	23 (11.4)	20 (10.0)
Day 15	88 (51.2)	36 (21.1)	31 (18.1)	71 (35.7)	49 (24.4)	33 (16.5)
Day 18	88 (51.2)	36 (21.1)	31 (18.1)	71 (35.7)	49 (24.4)	33 (16.5)

Source: Reviewer's Analysis.

3.2.4 Results and Conclusions

3.2.4.1 Efficacy Results

3.2.4.1.1 *Primary Efficacy Analysis*

The two pivotal studies (Studies 842 and 875) provided statistically significant efficacy evidence for a one drop three-times-a-day (TID) administration of Lotemax SM for the treatment of inflammation and pain following ocular surgery. The treatment difference (TID-Vehicle) in the proportion of subjects with complete resolution of anterior chamber cells at post-operative Day 8 was 19.4% (95% CI: 11.3%, 27.4%) in Study 842 and 10.4% (95% CI: 1.9%, 18.9%) in Study 875. Similarly, the differences (TID-Vehicle) in the proportion of subjects with complete resolution of ocular pain at post-operative Day 8 were 25.4% (95% CI: 15.4%, 35.4%) and 25.8% (95% CI: 16.6%, 34.9%) in Study 842 and Study 875, respectively (Table 10).

In contrast, only Study 842 provided statistically significant difference between Lotemax SM BID and Vehicle with respect to both efficacy endpoints. In Study 875, there was no statistically significant difference between Lotemax SM BID and Vehicle in the proportion of subjects with complete resolution of anterior chamber cells at Day 8. Consequently, because of the pre-specified testing procedure, no formal statistical conclusion could be made for the pain outcome in this study for Lotemax SM BID. However, the proportion of subjects with complete resolution of ocular pain at Day 8 in the Lotemax SM BID arm was consistent with the result of the Lotemax SM BID arm seen in Study 842, and the observed treatment difference (BID-Vehicle) is nominally significant. The treatment difference (BID-Vehicle) in the proportion of subjects with complete resolution of anterior chamber cells at post-operative Day 8 was 17.6% (95% CI: 9.7%, 25.5%) in Study 842 and 5.8% (95% CI: -3.6%, 15.2%) in Study 875. The differences (BID-Vehicle) in the proportion of subjects with complete resolution of ocular pain at post-operative Day 8 were 26.0% (95% CI: 16.0%, 36.0%) and 25.4% (95% CI: 14.9%, 35.9%) in Study 842 and Study 875, respectively (Table 10).

Table 10: Applicant's Primary Efficacy Analysis (ITT)

	Treatments			**% Diff (95% CI)**	
	Vehicle N=172	**BID N=171**	**TID N=171**	**BID- Vehicle**	**TID- Vehicle**
Outcome	**Study 842**				
ACC; n (%)	16 (9.3)	46 (26.9)	49 (28.7)	17.6 (9.7, 25.5)	19.4 (11.3, 27.4)
Pain: n (%)	82 (47.7)	126 (73.7)	125 (73.1)	26.0 (16.0, 36.0)	25.4 (15.4, 35.4)
	Study 875				
Outcome	**Vehicle N=199**	**BID N=201**	**TID N=200**	**BID- Vehicle**	**TID- Vehicle**
ACC; n (%)	40 (20.1)	52 (25.9)	61 (30.5)	5.8 (-3.6, 15.2)	10.4 (1.9, 18.9)
Pain: n (%)	99 (49.7)	151 (75.1)	151 (75.5)	25.4 (14.9, 35.9)	25.8 (16.6, 34.9)

Source: Table 6 of the Applicant's study reports. n=number of subjects with complete resolution; ACC: Anterior chamber cells; Pain: Ocular pain. Subjects who received rescue therapy prior to Day 8 and subjects with missing outcome are treated as treatment failures.

For study 875, the Applicant used a Bonferroni-based tree structured gatekeeping strategy to control the Type I error rate at 5%. In this approach, the test for the treatment differences were conducted hierarchically at 2.5% level. To align the significance level for the confidence interval estimates with the levels of significance used for the test (2.5%), this reviewer provided the 97.5% confidence interval for the treatment differences in Study 875. The efficacy conclusions remained the same (Table 11).

Table 11: Reviewer's Primary Efficacy Analysis Study 875 (ITT)

	Treatments			% Diff (97.5% CI)	
Outcome	Vehicle N=199	BID N=201	TID N=200	BID- Vehicle	TID- Vehicle
ACC; n (%)	40 (20.1)	52 (25.9)	61 (30.5)	5.8 (-3.6, 15.2)	10.4 (0.7, 20.1)
Pain: n (%)	99 (49.7)	151 (75.1)	151 (75.5)	25.4 (14.9, 35.9)	25.8 (15.3, 36.2)

Source: Reviewer's Analysis. ACC: Anterior chamber cells; Pain: Ocular pain. Subjects who received rescue therapy prior to Day 8 and subjects with missing outcome are treated as treatment failures.

3.2.4.1.1 *Sensitivity Analyses*

The Applicant's sensitivity analyses results presented in Table 12 are consistent with the results seen in the primary efficacy analyses. The Applicant's sensitivity analyses included the analysis of the primary efficacy endpoints on the per-protocol population with observed data only, and the analysis of the primary efficacy endpoints on the ITT population with all missing data including data after rescue use imputed using the LOCF approach. The Applicant also provided the proportion of subjects who achieved complete clearing of anterior chamber cells and proportion of subjects who achieved complete resolution of ocular pain on the final on-treatment visit. The final on-treatment visit included any visit including unscheduled visits while the subjects were on treatment excluding any post-rescue visits.

Table 12: Sensitivity Analysis Results for the Primary Efficacy Endpoints

	Study 842			Study 875		
Approaches	Vehicle N =172	TID N=171	Diff (95% CI)	Vehicle N=199	TID N=200	Diff (95% CI)
	Complete resolution of anterior chamber inflammation at Day 8					
Primary[1]	16/172 (9.3)	49/171 (28.7)	19.4 (11.3, 27.4)	40/199 (20.1)	61/200 (30.5)	10.4 (1.9, 18.9)
LOCF[2]	17/172 (9.9)	49 /171 (28.7)	18.8 (107, 26.9)	43/199 (21.6)	62/ 200 (31.0)	9.4 (0.8, 18.0)
Per-protocol[3]	13/113 (11.5)	43/141 (30.5)	19.0 (9.4, 28.6)	34/139 (24.5)	55/168 (32.7)	8.3 (-1.8, 18.3)
Final on-treatment[4]	29/172 (16.9)	84/170 (49.4)	32.6 (23.2, 41.9)	67/190 (35.3)	94/198 (47.5)	12.2 (2.5, 21.9)
	Complete Resolution of Ocular Pain at Day 8					
Primary[1]	82/172 (47.7)	125/171 (73.1)	26.0 (16.0, 36.0)	99/199 (49.7)	151/200 (75.5)	25.8 (16.6, 34.9)
LOCF[2]	95/172 (55.2)	131/171 (76.6)	21.4 (11.6, 31.1)	106/199 (53.3)	155/200 (77.5)	24.2 (15.2, 33.3)
Per-protocol[3]	73/113 (64.6)	113/141 (80.1)	15.5 (4.5, 26.5)	89/139 (64.0)	133/168 (79.2)	15.1 (5.1, 25.2)
Final on-treatment[4]	108/172 (62.8)	145/170 (85.3)	22.5 (13.5, 31.5)	122/190 (64.2)	170/198 (85.9)	21.6 (13.3, 30.0)

[1]Source: Adapted from Table 6 of the study reports. All missing data, including data collected after receiving rescue therapy, was treated as treatment failure. [2]Source: Adapted from Table 8 of the study report. All missing data including data after rescue medication was imputed using LOCF. [3]Source: Adapted from Table 7 of the study report. Only observed data among subjects who stayed in the study through Day 8 and have no major protocol violation was used. [4] Source: Adapted from Table 14.2.2.1.2 and Table 14.2.3.1.2 of the study reports. Data from the final on-treatment visit for each subject, including any unscheduled visits and excluding any post-rescue visits is used.

The reviewer provided the results of the same sensitivity analyses results (Table 13) with a 97.5% CI provided for the treatment differences in Study 875 for all sensitivity analyses approaches. In addition, randomized and treated subjects who did not have any pre-rescue data were excluded from the final on-treatment difference in the Applicant's summary. In line with

the analysis of the primary efficacy endpoint, the reviewer's summary treated these subjects as treatment failures. Except for the LOCF approach, for which the treatment difference for the anterior chamber cell outcome is no longer significant at 2.5% level of significance, the conclusions from the reviewer's summary are consistent with the sensitivity analysis results provided by the Applicant.

Table 13: Reviewer's Sensitivity Analysis Results for the Primary Efficacy Endpoints

	Study 842			Study 875		
Approaches	**Vehicle N =172**	**TID N=171**	**Diff (95% CI)**	**Vehicle N=199**	**TID N=200**	**Diff (97.5% CI)**
	Complete resolution of anterior chamber inflammation at Day 8					
Primary[1]	16/172 (9.3)	49/171 (28.7)	19.4 (11.3, 27.4)	40/199 (20.1)	61/200 (30.5)	10.4 (0.7, 20.1)
LOCF[2]	17/172 (9.9)	49 /171 (28.7)	18.8 (10.7, 26.9)	43/199 (21.6)	62/ 200 (31.0)	9.4 (-0.4, 19.2)
Per-protocol[3]	13/113 (11.5)	43/141 (30.5)	19.0 (9.4, 28.6)	35/139 (24.5)	55/168 (32.7)	8.3 (-3.2, 19.8)
Final on-treatment[4]	29/172 (16.9)	84/171 (49.1)	32.3 (21.6, 43.0)	67/199 (33.7)	94/200(47.0)	13.3 (2.4, 24.2)
	Complete Resolution of Ocular Pain at Day 8					
Primary[1]	82/172 (47.7)	125/171 (73.1)	26.0 (16.0, 36.0)	99/199 (49.7)	151/200 (75.5)	25.8 (15.3, 36.2)
LOCF[2]	95/172 (55.2)	131/171 (76.6)	21.4 (11.6, 31.1)	106/199 (53.3)	155/200 (77.5)	24.2 (13.9, 34.6)
Per-protocol[3]	73/113 (64.6)	113/141 (80.1)	15.5 (4.5, 26.5)	89/139 (64.0)	133/168 (79.2)	15.1 (3.6, 26.7)
Final on-treatment[4]	108/172 (62.8)	145/171 (84.8)	22.0 (12.7, 32.3)	122/199 (61.3)	170/200 (85.0)	23.7 (14.1, 33.3)

[1]Source: Adapted from Table 6 of the study reports. All missing data, including data collected after receiving rescue medication, was treated as treatment failure. [2]Source: Adapted from Table 8 of the study report. Missing data due to other reasons and data after rescue medication use was imputed using LOCF. [3]Source: Adapted from Table 7 of the study report. Only observed data among subjects who stayed in the study through Day 8 and have no major protocol violation was used. [4] Reviewer's Analysis. Data from the final on-treatment visit for each subject, including any unscheduled visits and excluding any post-rescue visits is used. Treated subjects with no efficacy outcome pre-rescue use are treated as treatment failures.

Reviewer's remarks: In summary, missing data was negligible in the primary efficacy analyses and the estimations of the treatment differences were done with minimal statistical assumptions. The results for the inflammation outcome from the LOCF analysis and the primary efficacy analysis are comparable. This is mostly because subjects who needed rescue therapy were subjects whose inflammation had either worsened or did not change compared to a prior visit. Thus, for most subjects, the LOCF inflammation scores from a pre-rescue visits were greater than zero (failure).

The analysis based on the per-protocol population excludes 34% and 17% of randomized subjects in the Vehicle and Lotemax SM TID arms, respectively in Study 842; and 30% and 16% of randomized subjects in the Vehicle and Lotemax SM TID arms in Study 875. The final-on-treatment visit treatment difference measures the treatment difference at any time within 15 days while the subjects are taking their respective drug. This is slightly different from the primary efficacy analysis estimate as this includes efficacy outcome from some subjects who received the study drug for more than 8 days (i.e. is not restricted to the effect of the study drug within 8 days of use).

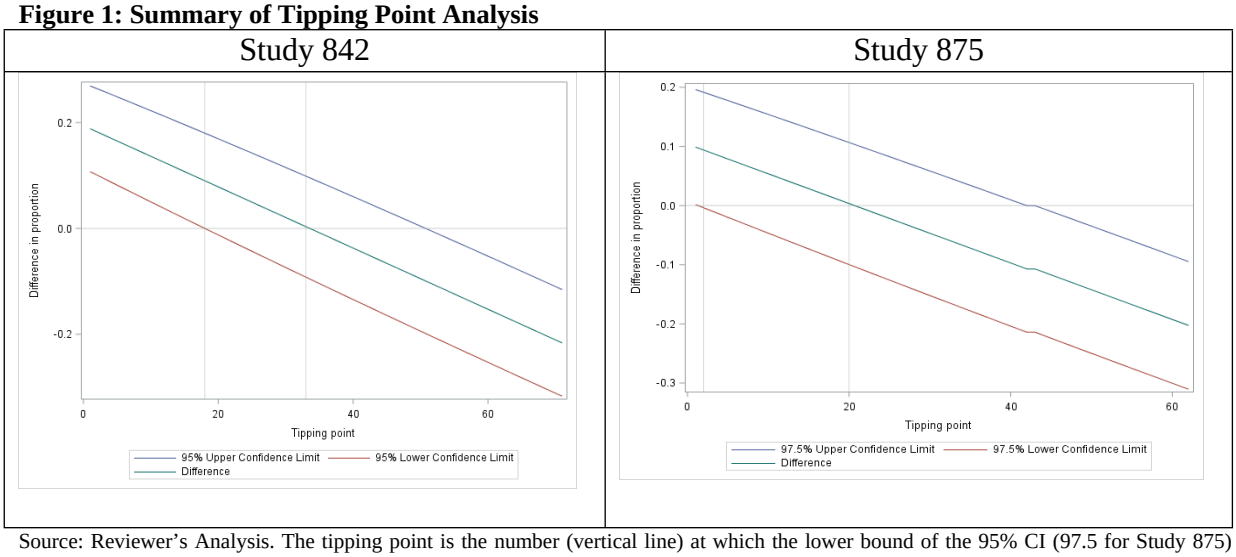
Tipping point Analysis

Very few subjects discontinued the study for reasons other than rescue therapy use (Table 6). On the other hand, rescue therapy was given to 51% and 35% of Vehicle randomized subjects in Study 842 and 875, respectively. Consequently, use of rescue therapy is the single intercurrent event of interest that could potentially impact the evaluation of efficacy significantly. The

reviewer therefore conducted a tipping point analysis to determine the number of subjects in the Vehicle arm who received a rescue therapy (and thus set as treatment failures) that need to be set as treatment successes for the treatment difference for the anterior chamber cells outcome to no longer be statistically significant. A larger tipping point implies that the result was only minimally impacted by subjects in the Vehicle arm who received a rescue medication and set as treatment failures.

In study 842, 18 or more of the 72 subjects who received a rescue therapy prior to Day 8 had to be set as treatment successes for the treatment difference (TID-Vehicle) to no longer be statistically significant. Additionally, at least 33 subjects need to be treated as treatment successes for the observed treatment difference to be negative (numerically unfavorable to Lotemax SM TID). In Study 875, because the treatment difference is slightly lower, if only 2 or more of the 62 subjects who received a rescue therapy and hence were treated as treatment failures were set as treatment successes, the treatment effect would no longer be statistically significant. The treatment difference however remains positive (favoring Lotemax SM TID) unless 20 or more Vehicle treated subjects who received rescue therapy are set as success (Figure 1).

Figure 1: Summary of Tipping Point Analysis



Source: Reviewer's Analysis. The tipping point is the number (vertical line) at which the lower bound of the 95% CI (97.5 for Study 875) is below zero.

Reviewer's remarks: The treatment difference (TID-Vehicle) in Study 875 (10.4%) is lower than in Study 842 (19.1%) mainly because of a larger success rate for subjects in the Vehicle arm in this study (9.3 vs 20.1). The proportion of subjects with complete clearing of anterior chamber cells in the Lotemax SM TID arms is in fact slightly higher in Study 875 than 842 (30.5% vs 28.7%).

3.2.4.1.2 *Secondary Efficacy Endpoints*

The results of the secondary efficacy endpoints are supportive of the primary efficacy analyses results. In both studies, the proportion of subjects with absence of ocular pain, anterior chamber cells and anterior chamber flare was consistently higher in the Lotemax SM arms at all the

efficacy evaluation visits (except on Day 3 in Study 842) with treatment differences ranging between 0% and 35%. The summary results are presented in Table 14 and Table 15 below and Figure 2-Figure 17 in the Appendix.

The summary of the anterior chamber inflammation and ocular pain categories at Day 8 is presented in Table 18 and Table 19, respectively. In these summaries, for subjects who received a rescue therapy on or prior to Day 8 and for those with missing outcome due to other reasons, the maximum observed inflammation category (4: >=30 cells) and the maximum observed pain score (5=Severe) are used. In the Vehicle arm, more than 73% of subjects in Study 842 and 59% in Study 875, had at least 6 anterior chamber cells in the study eye at Day 8. The corresponding figures for the Lotemax SM TID arm were 31% each in Study 842 and Study 875. The results also showed that, over 38% of subjects in the Lotemax SM TID arm had between 1-5 anterior chambers cells at Day 8. In both studies, the odds of having higher cell score (more number of cells) versus a lower number cells was at least 3 times higher for subjects in the Vehicle compared to those in the Lotemax SM TID [Odds Ratio (95% CI): 5.4 (3.5, 8.2); Study 842] and [Odds Ratio (95% CI): 2.8 (1.94, 4.0); Study 875].

Table 14: Proportion of Subjects with Clearing of the Anterior Chamber Cell by Visit (ITT: Study 842)

Visits	Treatments			Difference and 95% CI	
	Vehicle N=172	BID N=171	TID N=171	BID-Vehicle	TID-Vehicle
Day 3	12 (7%)	13 (8%)	7 (4%)	1% (-5%, 6%)	-3% (-8%, 2%)
Day 8	16 (9%)	46 (27%)	49 (29%)	18% (10%, 26%)	19% (11%, 27%)
Day 15	28 (16%)	73 (43%)	83 (49%)	26% (17%, 36%)	32% (23%, 42%)
Day 18	40 (23%)	77 (45%)	91 (53%)	22% (12%, 32%)	30% (20%, 40%)

Source: Table 14.2.2.1.2 of the study report. Subjects who received rescue medication prior to the evaluation of efficacy and subjects with missing anterior chamber cells outcome were treated as treatment failures.

Table 15: Proportion of Subjects with No Ocular Pain by Visit (ITT: Study 842)

Visits	Treatments			Difference and 95% CI	
	Vehicle N=172	BID N=171	TID N=171	BID-Vehicle	TID-Vehicle
Day 3	96 (56%)	123 (72%)	117 (68%)	16% (6%, 26%)	13% (2%, 23%)
Day 8	82 (48%)	126 (74%)	125 (73%)	26% (16%, 36%)	25% (15%, 35%)
Day 15	81(47%)	129 (75%)	137 (80%)	28% (18%, 38%)	33% (23%, 43%)
Day 18	73 (42%)	122 (71%)	122 (71%)	29% (19%, 39%)	29% (19%, 39%)

Source: Table 14.2.3.1.2 of the study report. Subjects who received rescue medication prior to the evaluation of efficacy and subjects with missing pain outcome were treated as treatment failures.

Table 16: Proportion of Subjects with Clearing of the Anterior Chamber Cell by Visit (ITT: Study 875)

Visits	Treatments			Difference and 95% CI	
	Vehicle N=199	BID N=201	TID N=200	BID-TID	TID-Vehicle
Day 3	9 (5%)	17 (8%)	9 (5%)	4% (-1%, 9%)	0% (-4%, 4%)
Day 8	40 (20%)	52 (26%)	61 (31%)	6% (-2%, 14%)	10% (2%, 19%)
Day 15	64 (32%)	80 (40%)	93 (47%)	8% (-2%, 17%)	14% (5%, 24%)
Day 18	73 (37%)	76 (38%)	95 (48%)	1% (-8%, 11%)	11% (1%, 20%)

Source: Table 14.2.2.1.2 of the study report. Subjects who received rescue medication prior to the evaluation of efficacy and subjects with missing anterior chamber cells outcome were treated as treatment failures.

Table 17: Proportion of Subjects with No Ocular Pain by Visit (ITT: Study 875)

	Treatments	Difference and 95% CI

Visits	Vehicle N=199	BID N=201	TID N=200	BID-TID	TID-Vehicle
Day 3	91 (46%)	143 (71%)	149 (75%)	25% (16%, 35%)	29% (20%, 38%)
Day 8	99 (50%)	151 (75%)	151 (76%)	25% (16%, 35%)	26% (17%, 35%)
Day 15	105(53%)	154 (77%)	158 (79%)	24% (15%, 33%)	26% (17%, 35%)
Day 18	107 (54%)	140 (70%)	145 (73%)	16% (6%, 25%)	19% (9%, 28%)

Source: Table 14.2.3.1.2 of the study report. Subjects who received rescue medication prior to the evaluation of efficacy and subjects with missing pain outcome were treated as treatment failures.

Table 18: Summary of Anterior Chamber Cell Category at Day 8 (ITT)

	Study 842			Study 875		
Category	Vehicle N =172	BID N=171	TID N=171	Vehicle N=199	BID N=201	TID N=200
None	16 (9.3)	45 (26.3)	49 (28.6)	39 (19.6)	52 (25.9)	61 (30.5)
1-5 cells	30 (17.4)	65 (38.0)	68 (39.8)	42 (21.1)	74 (38.6)	76 (38.0)
6-15 cells	34 (19.8)	30 (17.5)	26 (15.2)	40 (20.1)	41 (20.4)	34 (17.0)
16-30 cells	17 (9.9)	6 (3.5)	8 (4.7)	10 (5.0)	7 (3.5)	6 (3.0)
>30 cells	75 (43.6)	25 (14.6)	20 (11.7)	68 (34.2)	27 (13.4)	23 (11.5)

Source: Reviewer's Analysis. Subjects with missing outcome and those who received a rescue therapy were counted in the >30 cells category. One subject in the BID arm (Study 842) and one Subject in the Vehicle arm (Study 875) were not treated as treatment failures in the primary efficacy analysis despite receiving rescue therapy on or prior to Day 8. In this summary, they are counted in the ">30 cells" category

Table 19: Summary of Pain Category at Day 8 (ITT)

	Study 842			Study 875		
Category	Vehicle N =172	BID N=171	TID N=171	Vehicle N=199	BID N=201	TID N=200
None	71 (41.3)	121 (70.7)	122 (71.1)	87 (43.7)	143 (71.1)	144 (72.0)
Minimal	15 (8.7)	15 (8.8)	22 (12.9)	26 (13.1)	17 (8.5)	20 (10.0)
Mild	9 (5.2)	6 (3.5)	5 (2.9)	16 (8.0)	9 (4.5)	10 (5.0)
Moderate	2 (1.2)	3 (1.7)	2 (1.2)	3 (1.5)	6 (3.0)	3 (1.5)
Moderately Severe	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Severe	74 (43.0)	25 (14.6)	20 (11.7)	67 (33.7)	26 (12.9)	22 (11.0)

Source: Reviewer's Analysis. Subjects with missing outcome and those who received a rescue therapy were counted in the Severe category.

Note: The reviewer's results for the pain efficacy endpoint summarized above are slightly different from the applicant's results presented in the study reports. The applicant did not treat all subjects who received a rescue therapy for inflammation as treatment failures for the pain outcome. Consequently, the proportion of subjects with a pain score of zero (None) is slightly higher in the applicant's summary. However, most of the subjects who were not treated as treatment failure despite a rescue use were in the Vehicle arm. Consequently, the treatment differences with these subjects set as failures are more favorable to the Lotemax arms and lead to similar conclusions of a positive treatment effect.

3.3 Evaluation of Safety

In addition to the two pivotal studies (842 and 875), the submission included efficacy and safety summary from Study 843 (See Appendix for summary of Study 843). The safety summary thus is based on the pooled data from the three studies (842, 843 and 875). Note however that, because Study 843 only enrolled subjects to Vehicle and the Lotemax SM BID arms, the pooled safety data for the to-be-marketed Lotemax SM TID arm comes from the two pivotal studies (842 and 875) only. In the three studies combined, 535 subjects received Lotemax SM BID, 369 received Lotemax SM TID. The overall mean duration of exposure was 13.1 days (standard

deviation: 2.95) with a minimum of 1 and maximum of 18 days. The safety results showed a higher incidence of ocular adverse events in the Vehicle arm compared to the two Lotemax SM arms. A total of 40 (7%) subjects who receive Lotemax SM BID and 21 (6%) subjects who received Lotemax SM TID reported at least one ocular adverse event (AE) in the study eye compared to 67 (13%) subjects randomized to the Vehicle arm. The most frequently reported AEs among subjects who received the two Lotemax SM arms were photophobia, eye pain, and vitreous floater. No deaths were reported, and only one subject in the Lotemax SM BID arm reported serious adverse event compared to 3 subjects in the Vehicle arm (Table 20 and Table 21).

Table 20: Summary of Adverse Events

	Treatments			**Total**
Adverse Event	**Vehicle N=533**	**BID N=535**	**TID N=369**	**(BID+TID) N=904**
At least one AE (ocular and Non-ocular)	77 (14.4)	54 (10.1)	30 (8.1)	84 (9.3)
Any Serious AE (SAE)	3 (0.6)	1 (0.2)	0 (0.0)	1 (0.1)
At least one Ocular AE (Study eye)	67 (13)	40 (7)	21 (6)	61 (7)
Eye disorders	59 (11.1)	34 (6.4)	16 (4.3)	50 (5.5)
Photophobia	12 (2.3)	6 (1.1)	3 (0.8)	9 (1.0)
Eye pain	14 (2.6)	7 (1.3)	1 (0.3)	8 (0.9)
Vitreous floaters	0 (0.0)	5 (0.9)	1 (0.3)	6 (0.7)
Cystoid macular oedema	0 (0.0)	3 (0.6)	1 (0.3)	4 (0.4)
Lacrimation increased	4 (0.8)	3 (0.6)	0 (0.0)	3 (0.3)
Anterior chamber cell	0 (0.0)	1 (0.2)	1 (0.3)	2 (0.2)
Conjunctival hyperaemia	6 (1.1)	2 (0.4)	0 (0.0)	2 (0.2)
Eye discharge	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.2)
Eye inflammation	3 (0.6)	2 (0.4)	0 (0.0)	2 (0.2)
Eyelid ptosis	0 (0.0)	1 (0.2)	1 (0.3)	2 (0.2)
Macular oedema	1 (0.2)	2 (0.4)	0 (0.0)	2 (0.2)
Visual acuity reduced	3 (0.6)	2 (0.4)	0 (0.0)	2 (0.2)
Visual impairment	2 (0.4)	1 (0.2)	1 (0.3)	2 (0.2)
Anterior chamber flare	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Anterior chamber inflammation	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Ciliary hyperaemia	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.1)
Corneal disorder	2 (0.4)	1 (0.2)	0 (0.0)	1 (0.1)
Dry eye	1 (0.2)	0 (0.0)	1 (0.3)	1 (0.1)
Eye haemorrhage	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Eye pruritus	2 (0.4)	1 (0.2)	0 (0.0)	1 (0.1)
Eyelid irritation	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Eyelid oedema	3 (0.6)	0 (0.0)	1 (0.3)	1 (0.1)
Foreign body sensation in eyes	2 (0.4)	1 (0.2)	0 (0.0)	1 (0.1)
Iris neovascularisation	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Macular fibrosis	1 (0.2)	0 (0.0)	1 (0.3)	1 (0.1)
Photopsia	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Posterior capsule opacification	1 (0.2)	0 (0.0)	1 (0.3)	1 (0.1)
Retinal exudates	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Retinal haemorrhage	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Trichiasis	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Vitreous detachment	2 (0.4)	0 (0.0)	1 (0.3)	1 (0.1)
Conjunctival haemorrhage	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Conjunctival oedema	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Corneal oedema	9 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Eye irritation	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Eye oedema	4 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)

Iritis	4 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Ocular discomfort	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Ocular hyperaemia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Retinal degeneration	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Uveitis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Vision blurred	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	6 (1.1)	4 (0.7)	3 (0.8)	7 (0.8)
Sensation of foreign body	2 (0.4)	1 (0.2)	2 (0.6)	3 (0.3)
Instillation site pain	1 (0.2)	1 (0.2)	1 (0.3)	2 (0.2)
Adverse drug reaction	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Instillation site pruritus	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.1)
Pain	1 (0.2)	0 (0.0)	1 (0.3)	1 (0.1)
Instillation site erythema	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Instillation site foreign body sensation	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	1 (0.2)	2 (0.4)	2 (0.6)	4 (0.4)
Intraocular pressure increased	0 (0.0)	2 (0.4)	2 (0.6)	4 (0.4)
Intraocular pressure decreased	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Immune system disorders	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Drug hypersensitivity	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Infections and infestations	2 (0.4)	0 (0.0)	1 (0.3)	1 (0.1)
Hordeolum	2 (0.4)	0 (0.0)	1 (0.3)	1 (0.1)
Endophthalmitis	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Cataract operation complication	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Visual field defect	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Tables 12-15 of the study reports and Table 14.3.2.1 of the ISS.

Table 21: Serious Treatment-Emergent Adverse Events

Study	Subject Id	Treatment	Preferred Term	Location	Study Day		Severity
					Onset	Stop	
842	(b) (6)	Vehicle	Endophthalmitis	OD (Study eye)	Day 7	On going	Moderate
842		Lotemax SM BID	Small intestinal Obstruction	Non-ocular	Day 11	Day 16	Severe
843		Vehicle	Endophthalmitis	OD (Study eye)	Day 7	Day 19	Severe
875		Vehicle	Hypokalaemia	Non-ocular	Day 16	Day 18	Moderate

Source: Table 2.7.4.5-3 of summary-clin-safety.pdf located at \\Cdsesub1\evsprod\NDA208219\0001\m2. OD: oculus dexter (right eye)

4 Risk-benefit analysis

The risk benefit analysis presented in this section is based on the pooled data from the two Phase 3 studies (842 and 875). First, a subject is considered to have achieved a benefit if he/she achieved complete resolution of anterior chamber inflammation at Day 8. A risk refers to any ocular adverse event during the duration of the study. Overall, compared to Vehicle, Lotemax SM TID appears to have a favorable risk-benefit profile with respect to ocular adverse events. The proportion of subjects in the Lotemax SM TID arm who achieved clearing of the anterior chamber cells without reported ocular adverse event (Benefit +No risk) in the study eye was twice that of subjects in the Vehicle arm (29% vs. 14%). Only, 4 (1%) subjects from each arm who achieved complete clearing of the anterior chamber cell at Day 8 also reported at least one ocular adverse event during the study (Benefit + Risk). Twice as many subjects in the Vehicle arm reported at least one ocular adverse event without achieving complete clearance of the anterior chamber cells at Day 8 compared to the Lotemax SM TID arm (No Benefit +Risk). In

both arms, most subjects did not achieve complete clearance of the anterior chamber cells at Day 8 but also did not report any ocular adverse events during the study (No benefit + No Risk; Figure 18).

With benefit defined as achieving complete resolution of ocular pain at Day 8, the results show that a higher proportion of subjects in the Lotemax SM TID arm achieved complete resolution of ocular pain at Day 8 without reported ocular adverse event (Benefit +No risk) in the study eye compared to subjects in the Vehicle arm (70% vs. 46%). Only 16 (4%) subjects in the Lotemax SM TID arm and 11 (3%) in the Vehicle arm who achieved complete resolution of ocular pain at Day 8 also reported at least one ocular adverse event during the study (Benefit + Risk). Almost 7 times as many subjects in the Vehicle arm reported at least one ocular adverse event without achieving complete clearance of the anterior chamber cells at Day 8 compared to the Lotemax SM TID arm (No Benefit +Risk; Figure 19).

5 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The Applicant initially conducted a subgroup analyses for subgroups formed based on history of dry eye (Yes or No) and based on the sum of anterior chamber cells and anterior chamber flare at Day 1 (>=3 vs. <3) only. Upon an information request sent to them on September 25, 2018, they conducted and submitted subgroup analyses results for gender, race and iris color. Except for African American patients, the results of the subgroup analyses appear to be consistent with the results for the overall population.

For African American patients, the treatment difference is substantially lower than that of white patients in all studies and dose regimens except for the Lotemax SM BID dose in Study 842. For the to be marketed dose (TID), the treatment difference for African American (TID-Vehicle) is substantially lower than that of White and Asian patients in both studies that included the Lotemax SM TID arm (Study 842 and 875). The treatment difference in complete resolution of anterior chamber inflammation for African American patients is 9% (95% CI: -7%, 26%) in Study 842 and -21% (95% CI: -52%, 10%) in Study 875. The corresponding results for White patients are 22% (95% CI: 12%, 32%) in Study 842 and 14% (95% CI: 5%, 23%). For the overall population, the results are 19% (11%, 27%) and 10% (2%, 19%) in Study 842 and 875 respectively (Figure 20 and Figure 21). The same subgroup analysis was conducted by combining data from the two studies (Study 842 and Study 875). The treatment difference from this combined analysis for African American subgroup is -1% (95% CI: -17%, 16%; Figure 22).

For the Lotemax SM BID regimen, the treatment difference in complete resolution of anterior chamber inflammation for African American (BID-Vehicle) is higher compared to White and Asian patients in Study 842 (28% 95% CI (7%, 49%); Figure 26). However, the treatment difference is again the lowest at -21% (-52%, 10%, (Figures 5) in Study 875. The analysis conducted by combining data from Study 842 and Study 875 provides a treatment difference of -2% (95% CI: -14%, 11%; Figure 27). When the same analysis was conducted with data from all the three studies combined, the treatment difference (BID-Vehicle) is 3% (95% CI: -12%, 17%; Figure 28). Similar patterns were observed for the pain outcome.

Reviewer's Remarks: During the mid-cycle meeting, the clinical team communicated with the stat team that, dark colored iris is difficult to treat. Because this iris color is common in African American population, the lower efficacy result for African American subjects could be attributed to the iris color rather than differences in race.

6 SUMMARY AND CONCLUSIONS

6.1 Statistical Issues

There were no major statistical issues in the review of this application.

6.2 Collective evidence

The Applicant demonstrated a statistically significant efficacy of Lotemax SM TID against Vehicle in two adequate and well controlled trials. A higher proportion of subjects in the Lotemax SM TID arm achieved complete clearing of the anterior chamber cells and ocular pain at Day 8 compared to subjects randomized to the Vehicle arm. Besides, compared to the Lotemax SM TID arm, a higher number of subjects in the Vehicle arm needed a rescue therapy for inflammation. This could also be an indication that Lotemax SM TID had an anti-inflammatory effect. Additional supportive evidence for the efficacy of Lotemax SM TID was gained from the analyses of several secondary efficacy endpoints and sensitivity analyses on the primary efficacy endpoints.

In both studies, the proportion of subjects with ocular adverse events was higher in the Vehicle arm compared to the Lotemax SM arms. The most frequently reported AEs in the study eye for subjects who received Lotemax SM were photophobia, eye pain and vitreous floater. No deaths were reported, and only one subject in the Lotemax SM BID arm reported serious adverse event. The Lotemax SM TID arm also has a relatively favorable risk-benefit profile compared to Vehicle.

6.3 Labeling recommendation

The Applicant has the following text in section 14 (Clinical Trials) of the current version of the draft labeling:

"In two randomized, multicenter, double-masked, parallel-group, vehicle-controlled (b) (4) *in* (b) (4) *administered three times daily to the affected eye beginning the day after surgery was more effective compared to its vehicle in resolving anterior chamber inflammation and pain following cataract surgery.* (b) (4) *In these studies,* (b) (4) *had statistically significant higher* (b) (4) *of subjects with complete clearing of anterior chamber cells* (b) (4) *and of subjects who were pain free at Post-operative Day 8* (b) (4) *compared to vehicle."*

The percentage of subjects with completing clearing of inflammation and pain presented in the Applicant's draft labeling Section 14 (b) (4) This reviewer recommends that the results of each study be presented separately. In addition, it will also be informative to provide treatment differences and confidence intervals. This reviewer thus recommends the following text and efficacy summary for Section 14 of the drug labeling:

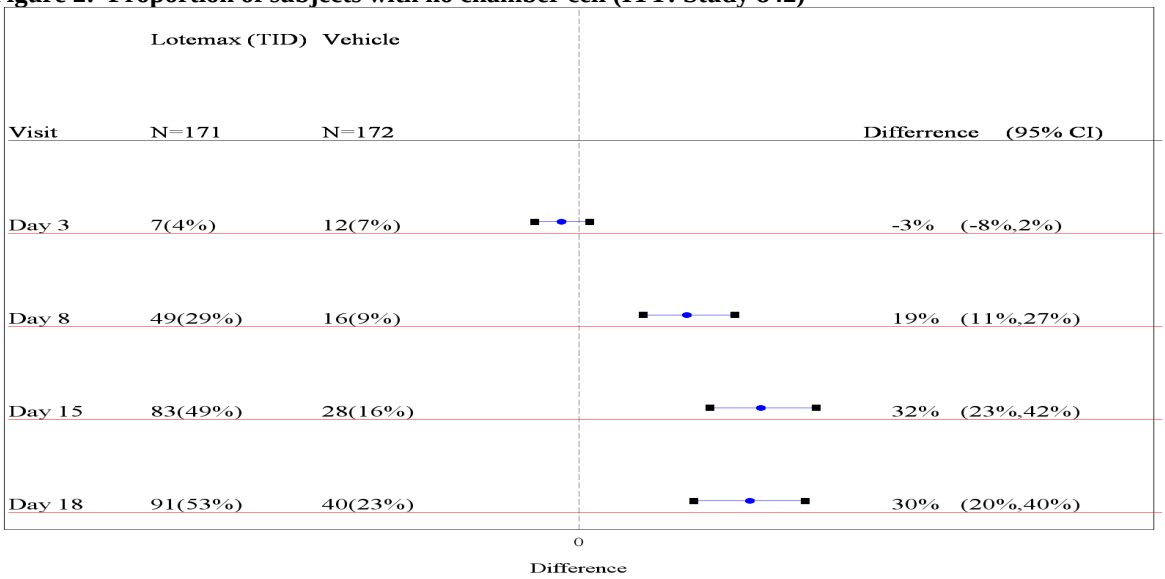
In two randomized, multicenter, double-masked, parallel group, vehicle-controlled trials, LOTEMAX SM administered three times daily to the affected eye beginning the day after surgery was more effective compared to its vehicle in resolving anterior chamber inflammation and pain following cataract surgery. In these studies, LOTEMAX SM had statistically significant higher incidences of subjects with complete clearing of anterior chamber cells and of subjects who were pain free at Post-operative Day 8 compared to vehicle. Results are shown in Table xx.

	Study 842			**Study 875**		
Outcome	Lotemax SM N=171 n (%)	Vehicle N=172 n (%)	Difference (95% CI)	Lotemax SM N=200 n (%)	Vehicle N=199 n (%)	Difference (95% CI)
(b) (4) Cells	49 (29)	16 (9)	19 (11, 27)	61 ((b) (4))	40 (20)	10 (2, 19)
(b) (4) pain	125 (73)	82 (48)	25 (15, 35)	151 ((b) (4))	99 (50)	26 (17, 35)

7 Appendix

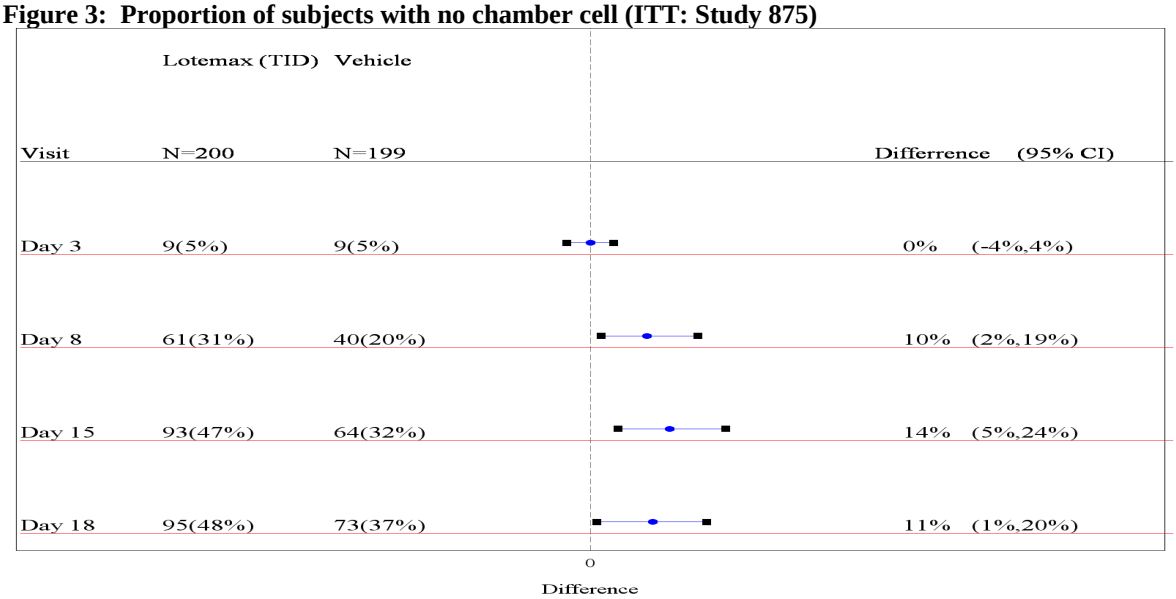
7.1 Selected Efficacy Summaries

Figure 2: Proportion of subjects with no chamber cell (ITT: Study 842)



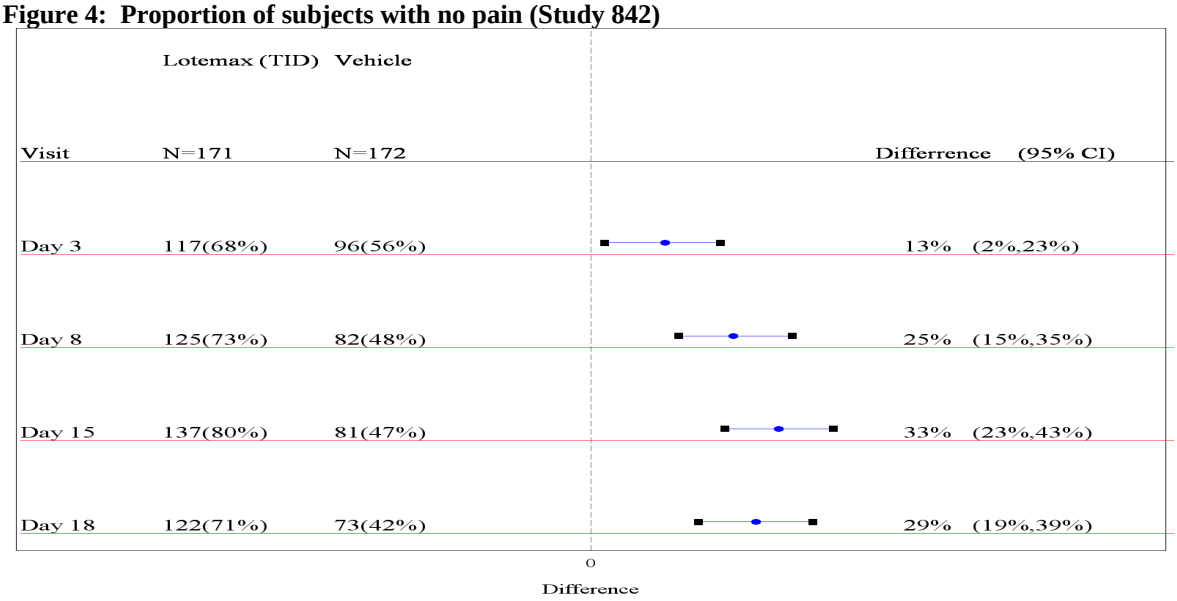
Source: Table 14.2.2.1.2 of the study report. Subjects who received rescue medication prior to the evaluation of efficacy and subjects with missing anterior chamber cells outcome were treated as treatment failures.

Figure 3: Proportion of subjects with no chamber cell (ITT: Study 875)



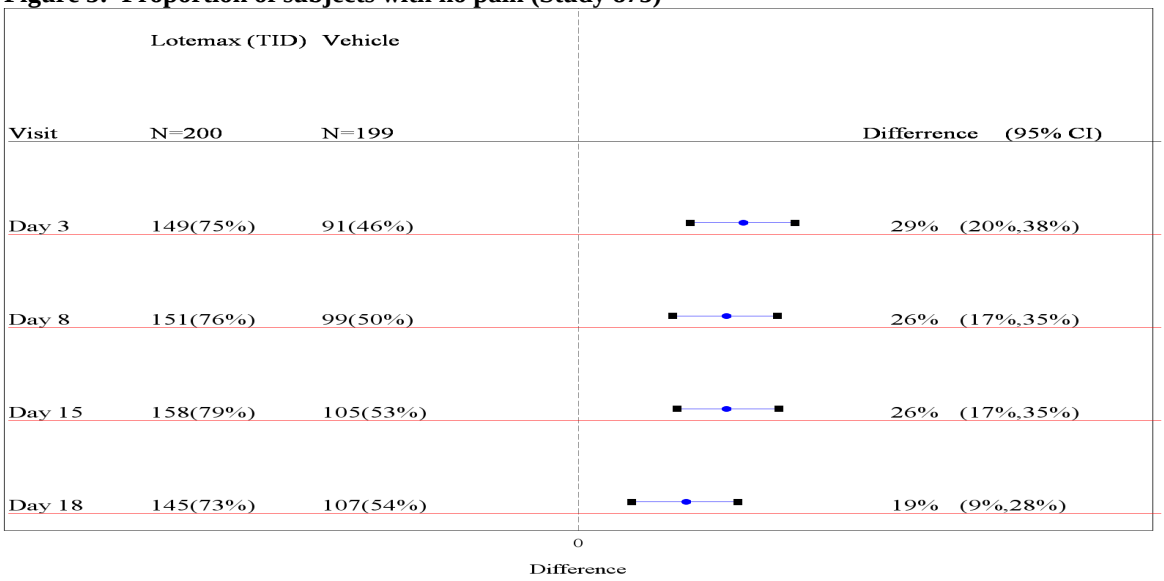
Source: Table 14.2.2.1.2 of the study report. Subjects who received rescue medication prior to the evaluation of efficacy and subjects with missing anterior chamber cells outcome were treated as treatment failures.

Figure 4: Proportion of subjects with no pain (Study 842)



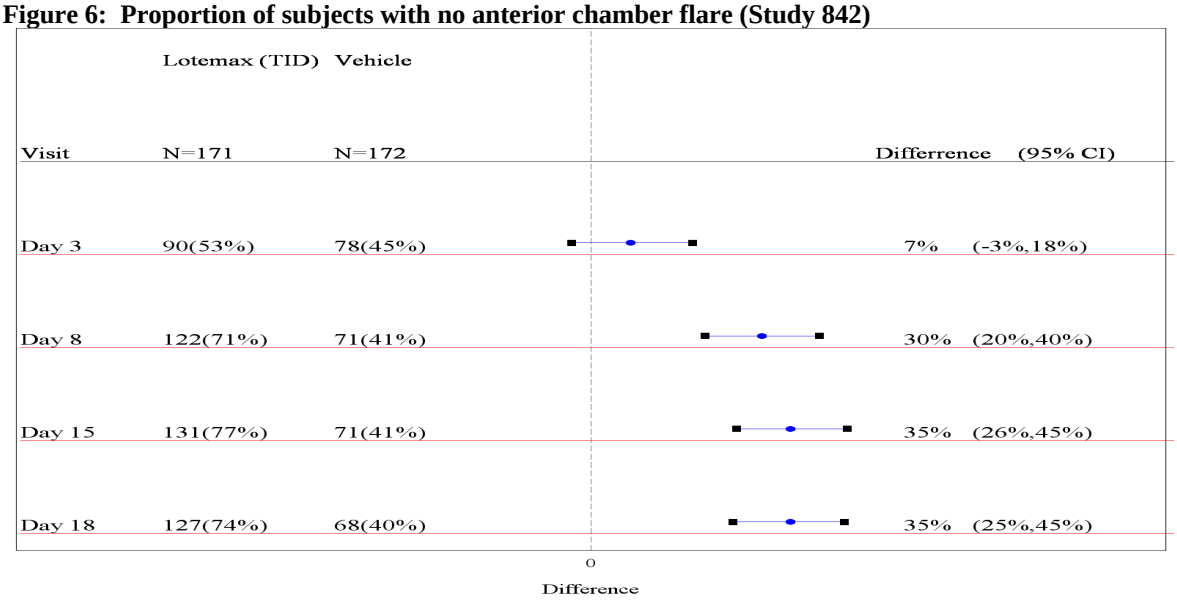
Source: Table 14.2.3.1.2 of the study report. Subjects who received rescue medication prior to the evaluation of efficacy and subjects with missing pain outcome were treated as treatment failures.

Figure 5: Proportion of subjects with no pain (Study 875)



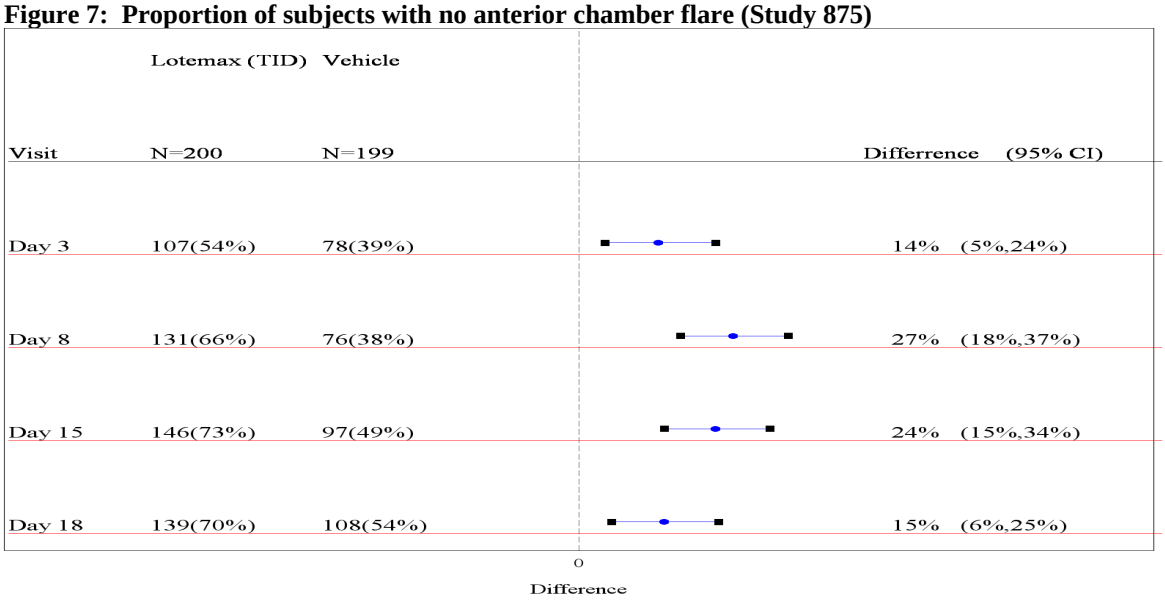
Source: Table 14.2.3.1.2 of the study report. Subjects who received rescue medication prior to the evaluation of efficacy and subjects with missing pain outcome were treated as treatment failures.

Figure 6: Proportion of subjects with no anterior chamber flare (Study 842)



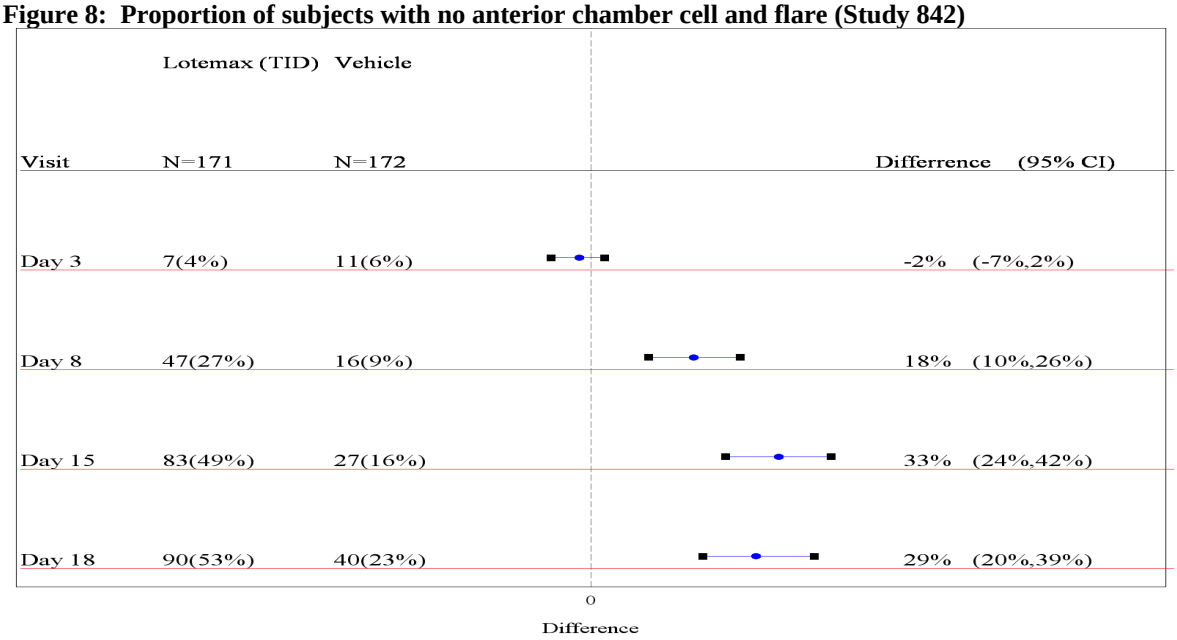
Source: Table 14.2.4.1.2 of the study report. Subjects who received rescue medication prior to the evaluation of efficacy and subjects with missing pain outcome were treated as treatment failures.

Figure 7: Proportion of subjects with no anterior chamber flare (Study 875)



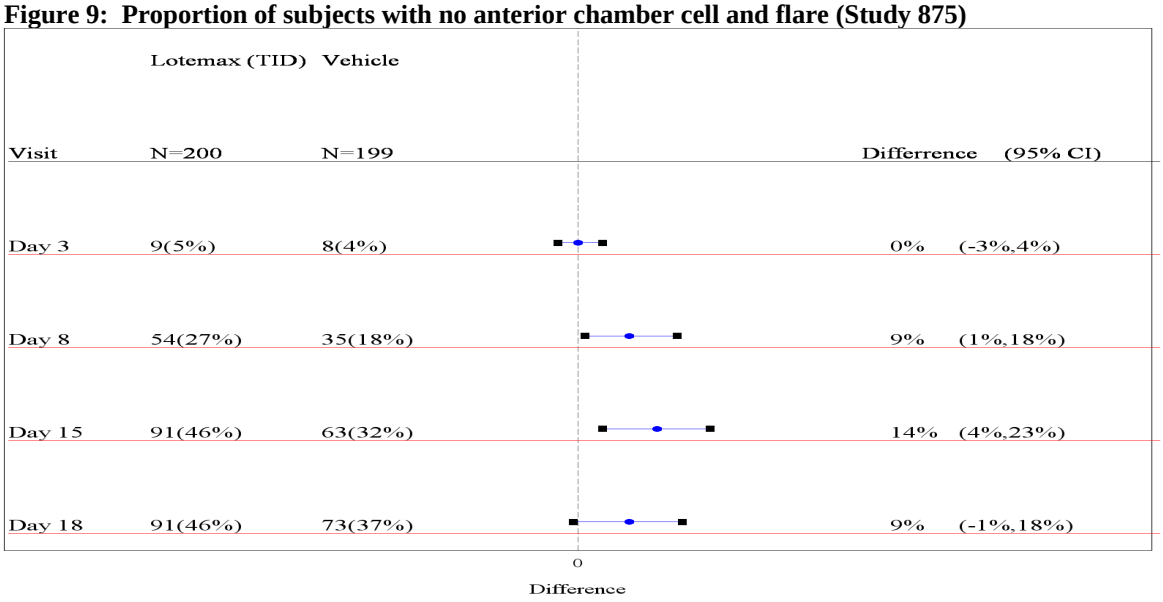
Source: Table 14.2.4.1.2 of the study report. Subjects who received rescue medication prior to the evaluation of efficacy and subjects with missing pain outcome were treated as treatment failures.

Figure 8: Proportion of subjects with no anterior chamber cell and flare (Study 842)



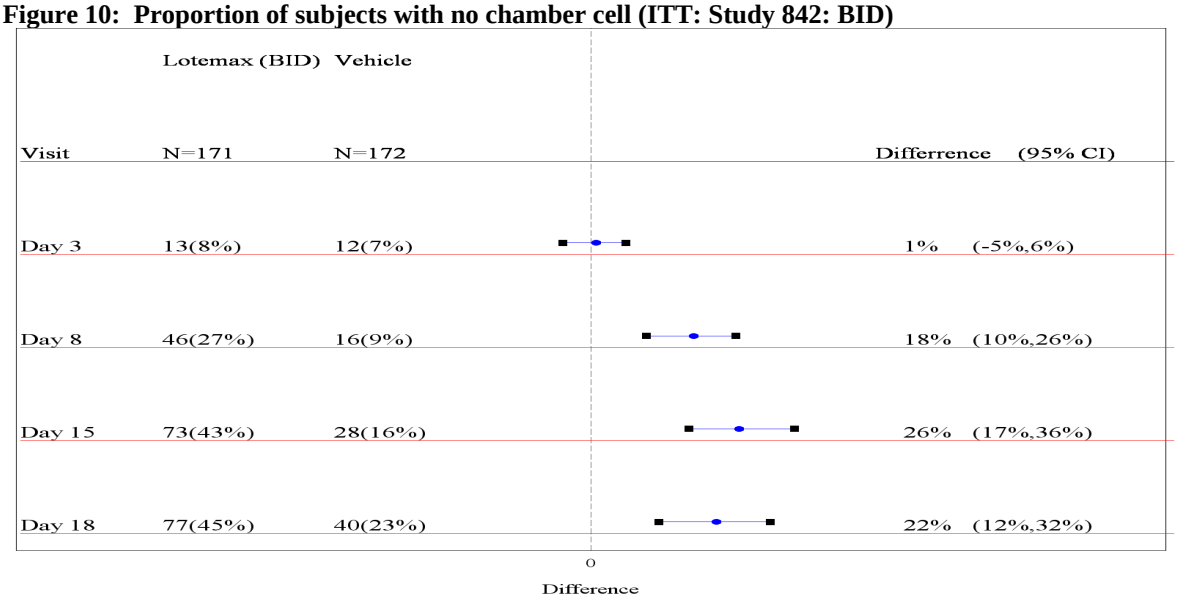
Source: Table 14.2.6.1.1 of the study reports Subjects who received a rescue therapy prior to time of evaluation were treated as treatment failure and subjects with missing data were imputed with LOCF

Figure 9: Proportion of subjects with no anterior chamber cell and flare (Study 875)



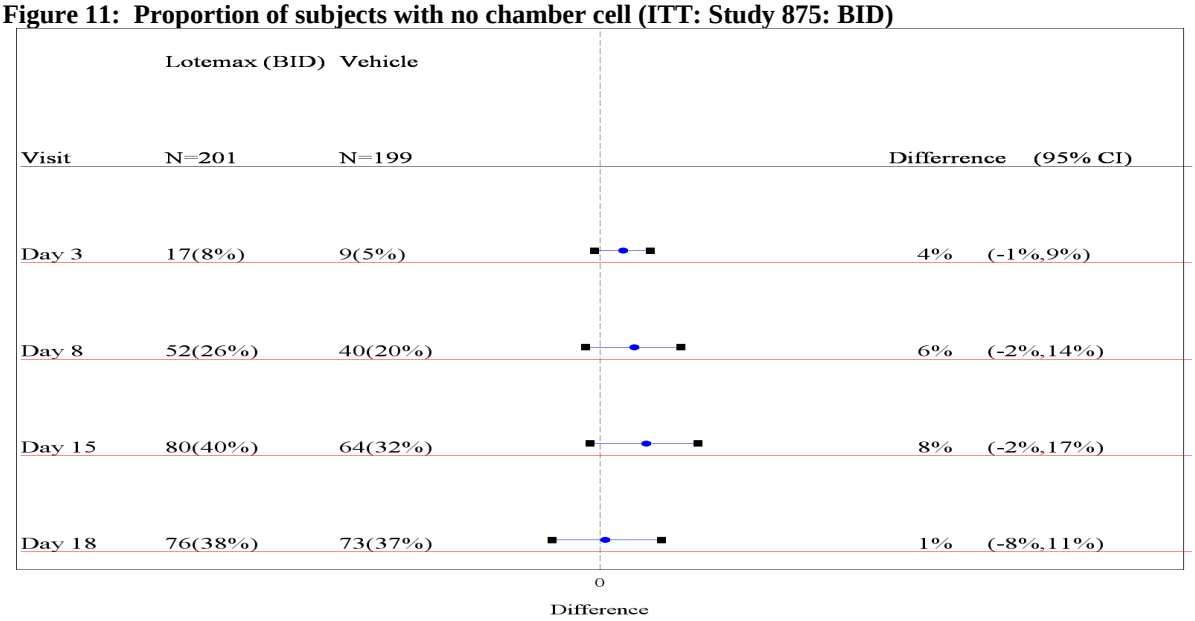
Source: Table 14.2.6.1.1 of the study reports Subjects who received a rescue therapy prior to time of evaluation were treated as treatment failure and subjects with missing data were imputed with LOCF

Figure 10: Proportion of subjects with no chamber cell (ITT: Study 842: BID)



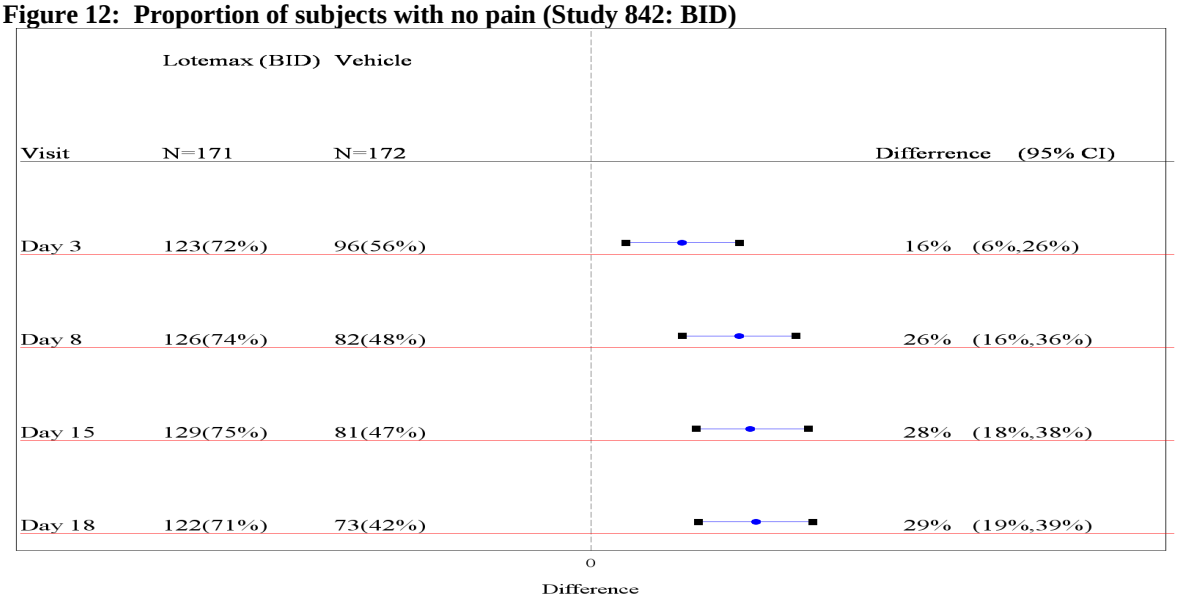
Source: Table 14.2.2.1.2 of the study report. Subjects who received rescue medication prior to the evaluation of efficacy and subjects with missing anterior chamber cells outcome were treated as treatment failures.

Figure 11: Proportion of subjects with no chamber cell (ITT: Study 875: BID)



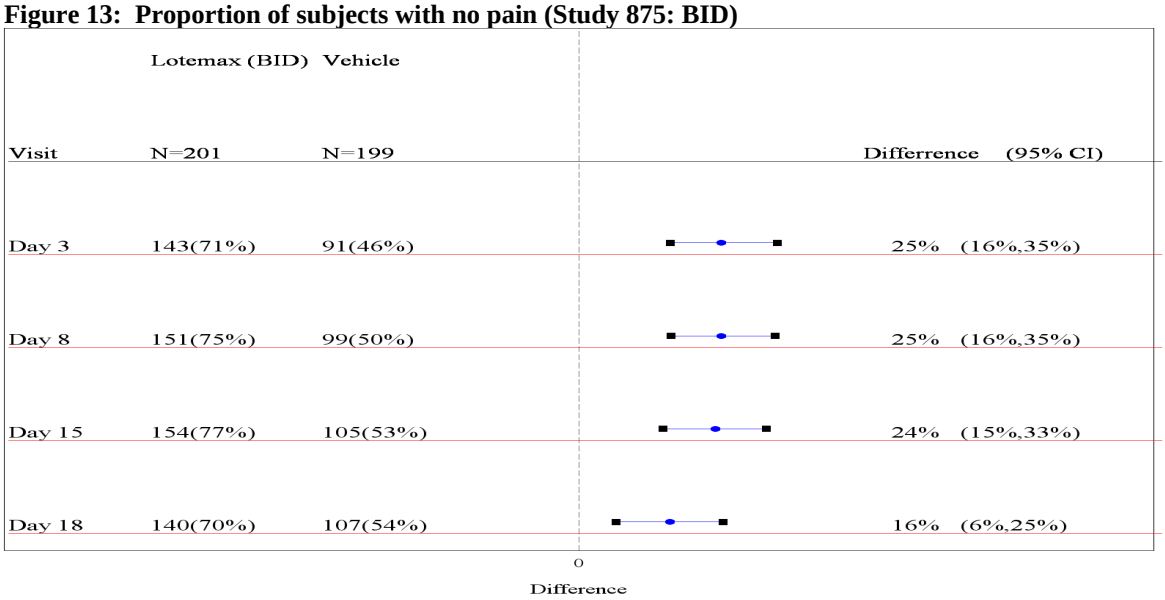
Source: Table 14.2.2.1.2 of the study report. Subjects who received rescue medication prior to the evaluation of efficacy and subjects with missing anterior chamber cells outcome were treated as treatment failures.

Figure 12: Proportion of subjects with no pain (Study 842: BID)



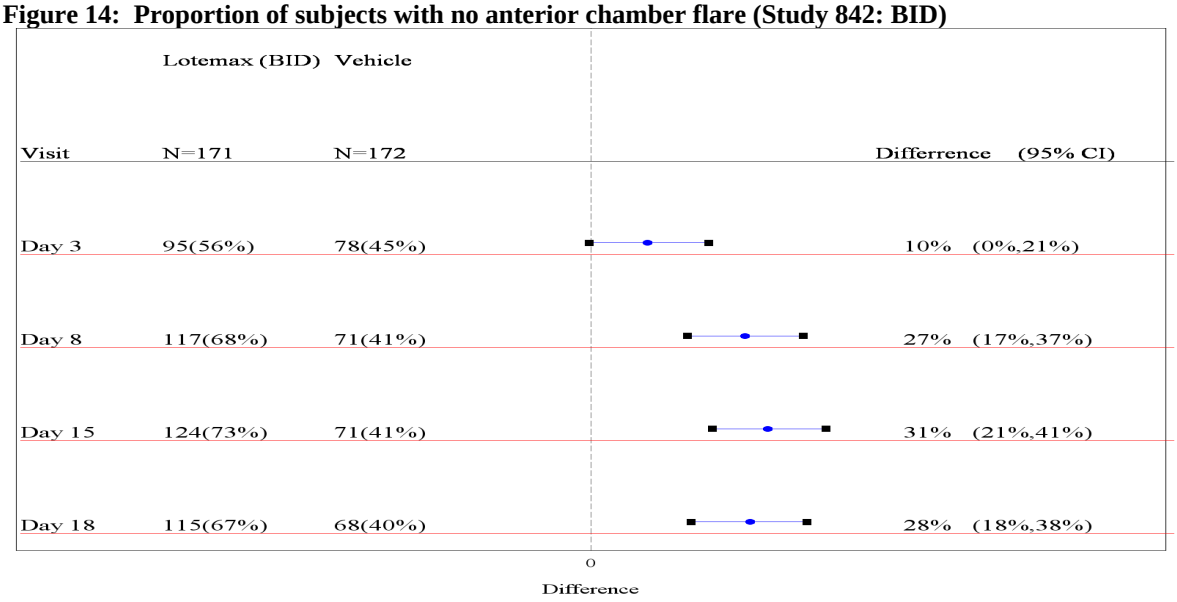
Source: Table 14.2.3.1.2 of the study report. Subjects who received rescue medication prior to the evaluation of efficacy and subjects with missing pain outcome were treated as treatment failures.

Figure 13: Proportion of subjects with no pain (Study 875: BID)



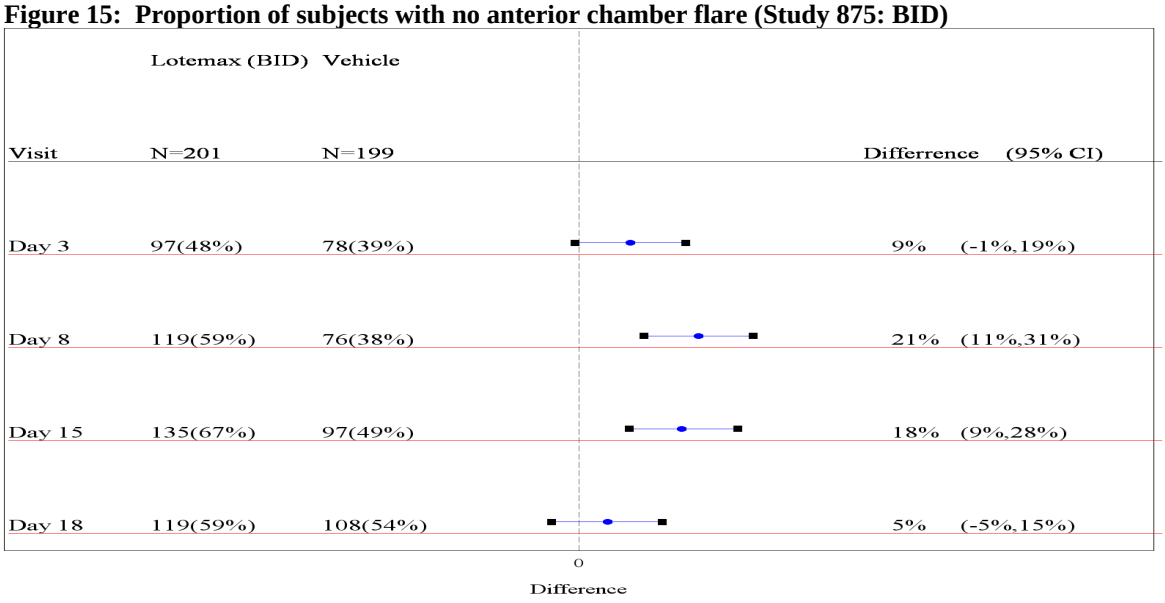
Source: Table 14.2.3.1.2 of the study report. Subjects who received rescue medication prior to the evaluation of efficacy and subjects with missing pain outcome were treated as treatment failures.

Figure 14: Proportion of subjects with no anterior chamber flare (Study 842: BID)



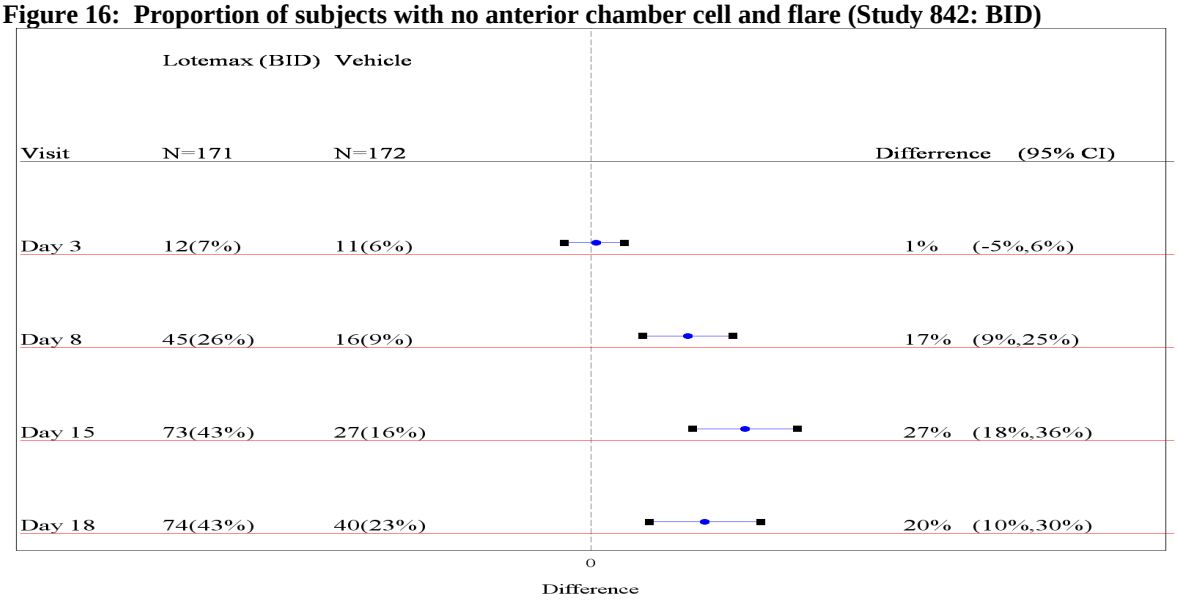
Source: Table 14.2.4.1.2 of the study report. Subjects who received rescue medication prior to the evaluation of efficacy and subjects with missing pain outcome were treated as treatment failures.

Figure 15: Proportion of subjects with no anterior chamber flare (Study 875: BID)



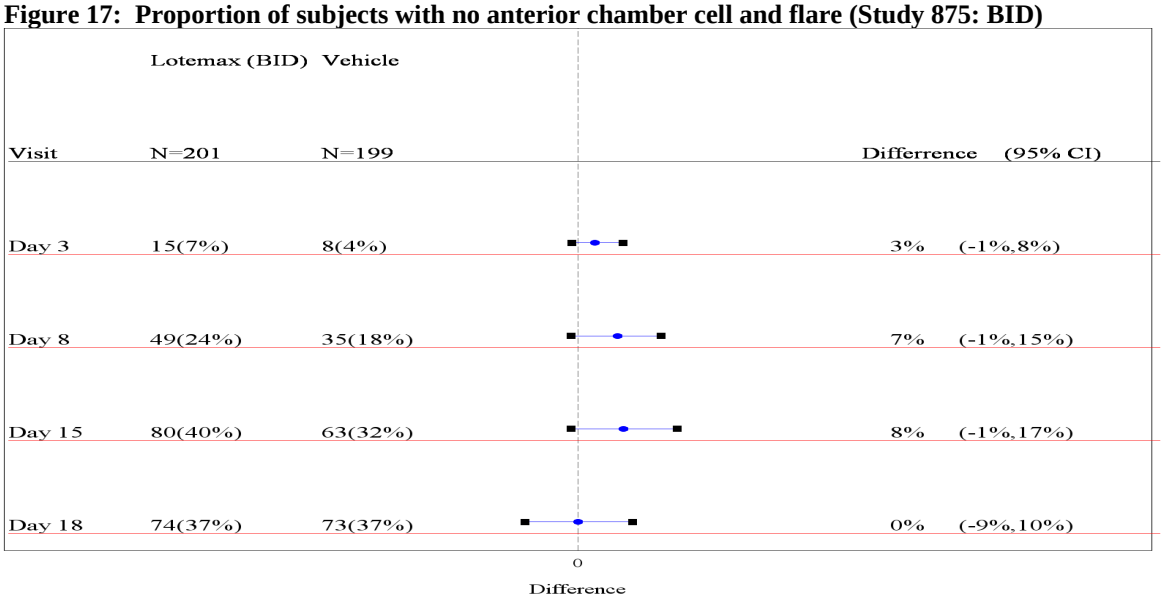
Source: Table 14.2.4.1.2 of the study report. Subjects who received rescue medication prior to the evaluation of efficacy and subjects with missing pain outcome were treated as treatment failures.

Figure 16: Proportion of subjects with no anterior chamber cell and flare (Study 842: BID)



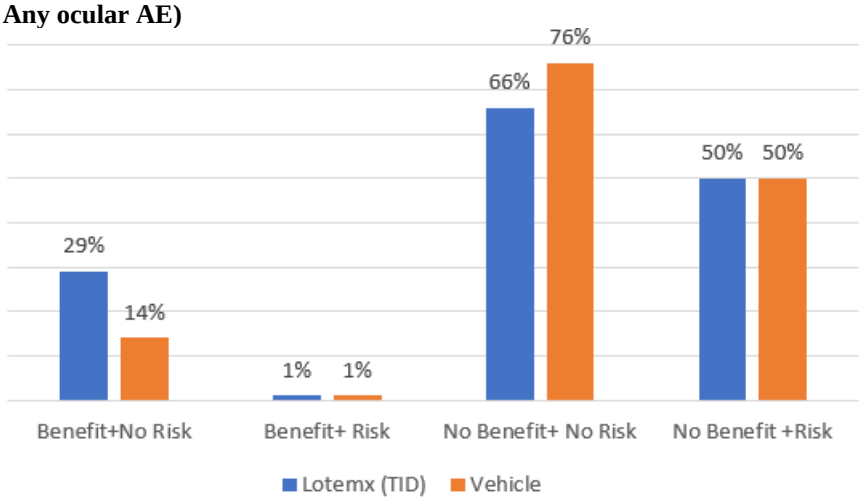
Source: Table 14.2.6.1.1 of the study reports Subjects who received rescue medication prior to the evaluation of efficacy were treated as treatment failure and subjects with missing data were imputed with LOCF

Figure 17: Proportion of subjects with no anterior chamber cell and flare (Study 875: BID)



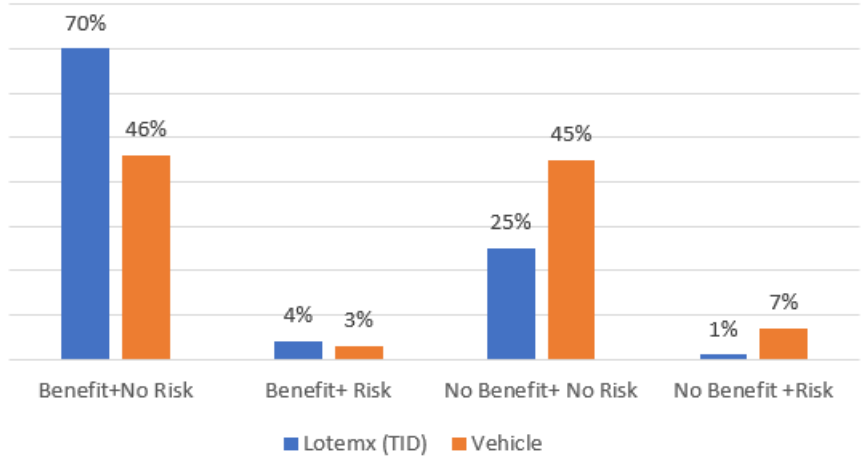
Source: Table 14.2.6.1.1 of the study reports Subjects who received rescue medication prior to the evaluation of efficacy were treated as treatment failure and subjects with missing data were imputed with LOCF

Figure 18: Summary of Benefit-Risk (Benefit= Complete clearing of anterior chamber cells at Day 8; Risk: Any ocular AE)



Source: Reviewer's Analysis. Subjects with missing data and subjects who received a rescue therapy prior to Day 8 are treated as treatment failures. ACC: anterior chamber cells

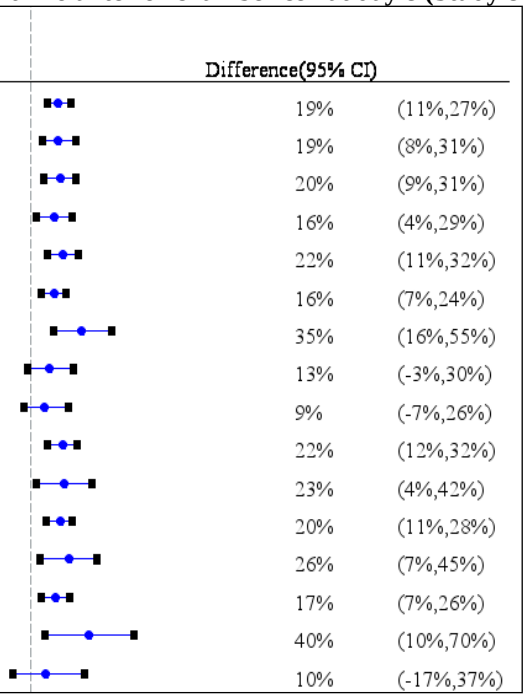
Figure 19: Summary of Benefit-Risk (Benefit= Complete clearing of ocular Pain score at Day 8; Risk: Any ocular AE)



Source: Reviewer's Analysis. Subjects with missing data and subjects who received a rescue therapy prior to Day 8 are treated as treatment failures.

Figure 20: Subgroup Analysis: Proportion of subjects with no anterior chamber cell at day 8 (Study 842)

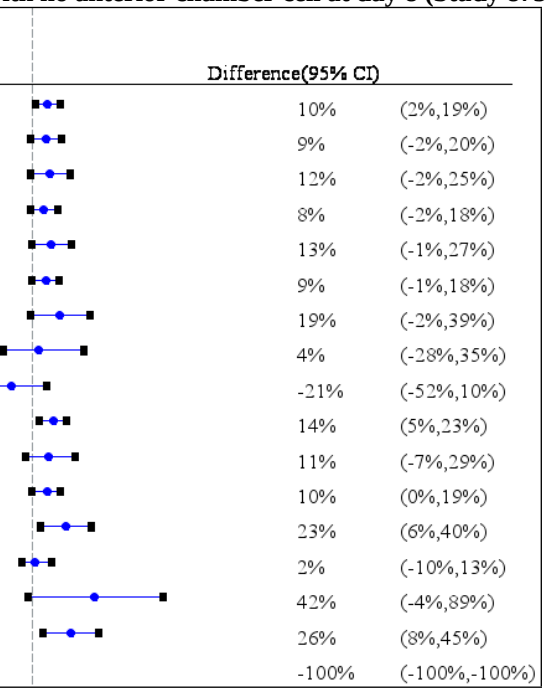
Subgroups	Lotemax TID n/N (%)	Vehicle n/N (%)	Difference(95% CI)	
Overall	49/171(29%)	16/172(9%)	19%	(11%,27%)
Sex: F	27/89(30%)	11/100(11%)	19%	(8%,31%)
Sex: M	22/82(27%)	5/72(7%)	20%	(9%,31%)
Age: <70	19/70(27%)	9/82(11%)	16%	(4%,29%)
Age: >=70	30/101(30%)	7/90(8%)	22%	(11%,32%)
History of Dry Eye: N	35/139(25%)	13/136(10%)	16%	(7%,24%)
History of Dry Eye: Y	14/32(44%)	3/36(8%)	35%	(16%,55%)
Race: ASIAN	4/24(17%)	1/29(3%)	13%	(-3%,30%)
Race: BLACK	3/22(14%)	1/24(4%)	9%	(-7%,26%)
Race: WHITE	42/125(34%)	14/119(12%)	22%	(12%,32%)
Day 1 ACC+ACF>=3: N	13/34(38%)	8/52(15%)	23%	(4%,42%)
Day 1 ACC+ACF>=3: Y	36/137(26%)	8/120(7%)	20%	(11%,28%)
Iris Color: BLUE	13/35(37%)	4/35(11%)	26%	(7%,45%)
Iris Color: BROWN	24/102(24%)	7/106(7%)	17%	(7%,26%)
Iris Color: GREEN	4/10(40%)	0/11(0%)	40%	(10%,70%)
Iris Color: HAZEL	8/23(35%)	5/20(25%)	10%	(-17%,37%)



Source: Adapted from Table 14.2.1.5 of the study reports and Table AHT1-AHT4 submitted as a response to information request. Subjects who received rescue therapy and those with missing data are treated as treatment failures

Figure 21: Subgroup Analysis: Proportion of subjects with no anterior chamber cell at day 8 (Study 875)

Subgroups	Lotemax TID n/N (%)	Vehicle n/N (%)	Difference(95% CI)	
Overall	61/200(31%)	40/199(20%)	10%	(2%,19%)
Sex: F	40/130(31%)	25/116(22%)	9%	(-2%,20%)
Sex: M	21/70(30%)	15/83(18%)	12%	(-2%,25%)
Age: <70	22/107(21%)	14/109(13%)	8%	(-2%,18%)
Age: >=70	39/93(42%)	26/90(29%)	13%	(-1%,27%)
History of Dry Eye: N	46/164(28%)	31/160(19%)	9%	(-1%,18%)
History of Dry Eye: Y	15/36(42%)	9/39(23%)	19%	(-2%,39%)
Race: ASIAN	4/14(29%)	4/16(25%)	4%	(-28%,35%)
Race: BLACK	5/23(22%)	6/14(43%)	-21%	(-52%,10%)
Race: WHITE	52/163(32%)	30/169(18%)	14%	(5%,23%)
Day 1 ACC+ACF>=3: N	20/55(36%)	11/44(25%)	11%	(-7%,29%)
Day 1 ACC+ACF>=3: Y	41/145(28%)	29/155(19%)	10%	(0%,19%)
Iris Color: Blue	19/49(39%)	8/50(16%)	23%	(6%,40%)
Iris Color: Brown	29/112(26%)	27/111(24%)	2%	(-10%,13%)
Iris Color: Green	3/5(60%)	3/17(18%)	42%	(-4%,89%)
Iris Color: Hazel	10/32(31%)	1/20(5%)	26%	(8%,45%)
Iris Color: Other	0/2(0%)	1/1(100%)	-100%	(-100%,-100%)



Source: Adapted from Table 14.2.1.5 of the study reports and Table AHT1-AHT4 submitted as a response to information request. Subjects who received rescue therapy and those with missing data are treated as treatment failures

Figure 22: Subgroup Analysis: Proportion of subjects with no anterior chamber cell at day 8 (Study 842+875)

Subgroups	Lotemax TID n/N (%)	Vehicle n/N (%)	Difference(95% CI)	
Overall	110/371(30%)	56/371(15%)	15%	(9%,20%)
Sex: F	67/219(31%)	36/216(17%)	14%	(6%,22%)
Sex: M	43/152(28%)	20/155(13%)	15%	(6%,24%)
Age: <70	41/177(23%)	23/191(12%)	11%	(3%,19%)
Age: >=70	69/194(36%)	33/180(18%)	17%	(8%,26%)
History of Dry Eye: N	81/303(27%)	44/296(15%)	12%	(5%,18%)
History of Dry Eye: Y	29/68(43%)	12/75(16%)	27%	(12%,41%)
Race: ASIAN	8/38(21%)	5/45(11%)	10%	(-6%,26%)
Race: BLACK	8/45(18%)	7/38(18%)	-1%	(-17%,16%)
Race: WHITE	94/288(33%)	44/288(15%)	17%	(11%,24%)
Day 1 ACC+ACF>=3: N	33/89(37%)	19/96(20%)	17%	(4%,30%)
Day 1 ACC+ACF>=3: Y	77/282(27%)	37/275(13%)	14%	(7%,20%)
Iris Color: BLUE	32/84(38%)	12/85(14%)	24%	(11%,37%)
Iris Color: BROWN	53/214(25%)	34/217(16%)	9%	(2%,17%)
Iris Color: GREEN	7/15(47%)	3/28(11%)	36%	(8%,64%)
Iris Color: HAZEL	18/55(33%)	6/40(15%)	18%	(1%,34%)
Iris Color: OTHER	0/3(0%)	1/1(100%)	-100%	(-100%,-100%)

Source: Reviewer's Analysis. Subjects who received rescue therapy and those with missing data are treated as treatment failures

Figure 23: Subgroup Analysis: Proportion of subjects with no pain at day 8 (Study 842)

Subgroups	Lotemax TID n/N (%)	Vehicle n/N (%)	Difference(95% CI)	
Overall	125/171(73%)	82/172(48%)	25%	(15%,35%)
Sex: F	63/89(71%)	46/100(46%)	25%	(11%,38%)
Sex: M	62/82(76%)	36/72(50%)	26%	(11%,40%)
Age: <70	49/70(70%)	36/82(44%)	26%	(11%,41%)
Age: >=70	76/101(75%)	46/90(51%)	24%	(11%,37%)
History of Dry Eye: N	103/139(74%)	63/136(46%)	28%	(17%,39%)
History of Dry Eye: Y	22/32(69%)	19/36(53%)	16%	(-7%,39%)
Race: ASIAN	17/24(71%)	13/29(45%)	26%	(0%,52%)
Race: BLACK	15/22(68%)	10/24(42%)	27%	(-1%,54%)
Race: WHITE	93/125(74%)	59/119(50%)	25%	(13%,37%)
Day 1 ACC+ACF>=3: N	29/34(85%)	24/52(46%)	39%	(21%,57%)
Day 1 ACC+ACF>=3: Y	96/137(70%)	58/120(48%)	22%	(10%,34%)
Iris Color: BLUE	25/35(71%)	18/35(51%)	20%	(-2%,42%)
Iris Color: BROWN	76/102(75%)	49/106(46%)	28%	(16%,41%)
Iris Color: GREEN	8/10(80%)	4/11(36%)	44%	(6%,81%)
Iris Color: HAZEL	15/23(65%)	11/20(55%)	10%	(-19%,39%)
Iris Color: OTHER	1/1(100%)			(,)

Source: Adapted from Table 14.2.1.5 of the study reports and Table AHT1-AHT4 submitted as a response to information request. Subjects who received rescue therapy and those with missing data are treated as treatment failures

Figure 24: Subgroup Analysis: Proportion of subjects with no pain at day 8 (Study 875)

Subgroups	Loteprednol TID n/N (%)	Vehicle n/N (%)	Difference(95% CI)	
Overall	151/200(76%)	99/199(50%)	26%	(17%,35%)
Sex: F	99/130(76%)	57/116(49%)	27%	(15%,39%)
Sex: M	52/70(74%)	42/83(51%)	24%	(9%,39%)
Age: <70	72/107(67%)	49/109(45%)	22%	(9%,35%)
Age: >=70	79/93(85%)	50/90(56%)	29%	(17%,42%)
History of Dry Eye: N	119/164(73%)	77/160(48%)	24%	(14%,35%)
History of Dry Eye: Y	32/36(89%)	22/39(56%)	32%	(14%,51%)
Race: ASIAN	8/14(57%)	10/16(63%)	-5%	(-40%,30%)
Race: BLACK	17/23(74%)	7/14(50%)	24%	(-8%,56%)
Race: WHITE	126/163(77%)	82/169(49%)	29%	(19%,39%)
Day 1 ACC+ACF>=3: N	40/55(73%)	25/44(57%)	16%	(-3%,35%)
Day 1 ACC+ACF>=3: Y	111/145(77%)	74/155(48%)	29%	(18%,39%)
Iris Color: Blue	30/49(61%)	28/50(56%)	5%	(-14%,25%)
Iris Color: Brown	85/112(76%)	57/111(51%)	25%	(12%,37%)
Iris Color: Green	5/5(100%)	8/17(47%)	53%	(29%,77%)
Iris Color: Hazel	29/32(91%)	5/20(25%)	66%	(44%,87%)
Iris Color: Other	2/2(100%)	1/1(100%)		(,)

Source: Adapted from Table 14.2.1.5 of the study reports and Table AHT1-AHT4 submitted as a response to information request. Subjects who received rescue therapy and those with missing data are treated as treatment failures

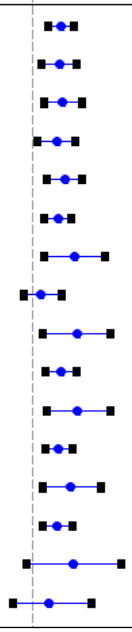
Figure 25: Subgroup Analysis: Proportion of subjects with no pain at day 8 (Study 842+875)

Subgroups	Loteprednol TID n/N (%)	Vehicle n/N (%)	Difference(95% CI)	
Overall	276/371(74%)	181/371(49%)	26%	(19%,32%)
Sex: F	162/219(74%)	103/216(48%)	26%	(17%,35%)
Sex: M	114/152(75%)	78/155(50%)	25%	(14%,35%)
Age: <70	121/177(68%)	85/191(45%)	24%	(14%,34%)
Age: >=70	155/194(80%)	96/180(53%)	27%	(17%,36%)
History of Dry Eye: N	222/303(73%)	140/296(47%)	26%	(18%,34%)
History of Dry Eye: Y	54/68(79%)	41/75(55%)	25%	(10%,40%)
Race: ASIAN	25/38(66%)	23/45(51%)	15%	(-6%,36%)
Race: BLACK	32/45(71%)	17/38(45%)	26%	(6%,47%)
Race: WHITE	219/288(76%)	141/288(49%)	27%	(19%,35%)
Day 1 ACC+ACF>=3: N	69/89(78%)	49/96(51%)	26%	(13%,40%)
Day 1 ACC+ACF>=3: Y	207/282(73%)	132/275(48%)	25%	(18%,33%)
Iris Color: BLUE	55/84(65%)	46/85(54%)	11%	(-3%,26%)
Iris Color: BROWN	161/214(75%)	106/217(49%)	26%	(18%,35%)
Iris Color: GREEN	13/15(87%)	12/28(43%)	44%	(19%,69%)
Iris Color: HAZEL	44/55(80%)	16/40(40%)	40%	(22%,58%)
Iris Color: OTHER	3/3(100%)	1/1(100%)		(,)

Source: Reviewer's Analysis. Subjects who received rescue therapy and those with missing data are treated as treatment failures

Figure 26: Subgroup Analysis: Proportion of subjects with no anterior chamber cell at day 8 (Study 842: BID)

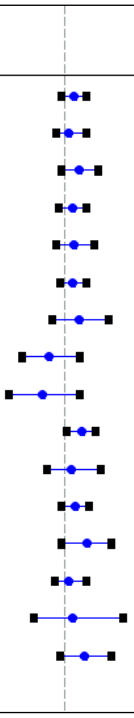
Subgroups	Lotemax BID n/N (%)	Vehicle n/N (%)	Difference(95% CI)	
Overall	46/171(27%)	16/172(9%)	18%	(10%,26%)
Sex: F	26/94(28%)	11/100(11%)	17%	(6%,28%)
Sex: M	20/77(26%)	5/72(7%)	19%	(8%,30%)
Age: <70	20/77(26%)	9/82(11%)	15%	(3%,27%)
Age: >=70	26/94(28%)	7/90(8%)	20%	(9%,30%)
History of Dry Eye: N	35/139(25%)	13/136(10%)	16%	(7%,24%)
History of Dry Eye: Y	11/32(34%)	3/36(8%)	26%	(7%,45%)
Race: ASIAN	2/23(9%)	1/29(3%)	5%	(-8%,19%)
Race: BLACK	7/22(32%)	1/24(4%)	28%	(7%,49%)
Race: WHITE	37/126(29%)	14/119(12%)	18%	(8%,27%)
Day 1 ACC+ACF>=3: N	14/32(44%)	8/52(15%)	28%	(9%,48%)
Day 1 ACC+ACF>=3: Y	32/139(23%)	8/120(7%)	16%	(8%,25%)
Iris Color: BLUE	14/39(36%)	4/35(11%)	24%	(6%,43%)
Iris Color: BROWN	22/100(22%)	7/106(7%)	15%	(6%,25%)
Iris Color: GREEN	2/8(25%)	0/11(0%)	25%	(-5%,55%)
Iris Color: HAZEL	8/23(35%)	5/20(25%)	10%	(-17%,37%)



Source: Adapted from Table 14.2.1.5 of the study reports and Table AHT1-AHT4 submitted as a response to information request. Subjects who received rescue therapy and those with missing data are treated as treatment failures

Figure 27: Subgroup Analysis: Proportion of subjects with no anterior chamber cell at day 8 (Study 875: BID)

Subgroups	Lotemax BID n/N (%)	Vehicle n/N (%)	Difference(95% CI)	
Overall	52/201(26%)	40/199(20%)	6%	(-2%,14%)
Sex: F	29/117(25%)	25/116(22%)	3%	(-8%,14%)
Sex: M	23/84(27%)	15/83(18%)	9%	(-3%,22%)
Age: <70	18/103(17%)	14/109(13%)	5%	(-5%,14%)
Age: >=70	34/98(35%)	26/90(29%)	6%	(-7%,19%)
History of Dry Eye: N	40/163(25%)	31/160(19%)	5%	(-4%,14%)
History of Dry Eye: Y	12/38(32%)	9/39(23%)	9%	(-11%,28%)
Race: ASIAN	2/20(10%)	4/16(25%)	-15%	(-40%,10%)
Race: BLACK	5/23(22%)	6/14(43%)	-21%	(-52%,10%)
Race: WHITE	45/158(28%)	30/169(18%)	11%	(2%,20%)
Day 1 ACC+ACF>=3: N	10/35(29%)	11/44(25%)	4%	(-16%,23%)
Day 1 ACC+ACF>=3: Y	42/166(25%)	29/155(19%)	7%	(-2%,16%)
Iris Color: BLUE	14/47(30%)	8/50(16%)	14%	(-3%,30%)
Iris Color: BROWN	31/115(27%)	27/111(24%)	3%	(-9%,14%)
Iris Color: GREEN	2/9(22%)	3/17(18%)	5%	(-28%,37%)
Iris Color: HAZEL	5/28(18%)	1/20(5%)	13%	(-4%,30%)
Iris Color: OTHER	0/2(0%)	1/1(100%)	-100%	(-100%,-100%)



Source: Adapted from Table 14.2.1.5 of the study reports and Table AHT1-AHT4 submitted as a response to information request. Subjects who received rescue therapy and those with missing data are treated as treatment failures

Figure 28: Subgroup Analysis: Proportion of subjects with no anterior chamber cell at day 8 (Study 842+875: BID)

Subgroups	Lotemax BID n/N (%)	Vehicle n/N (%)	Difference(95% CI)	
Overall	98/372(26%)	56/371(15%)	11%	(5%,17%)
Sex: F	55/211(26%)	36/216(17%)	9%	(2%,17%)
Sex: M	43/161(27%)	20/155(13%)	14%	(5%,22%)
Age: <70	38/180(21%)	23/191(12%)	9%	(2%,17%)
Age: >=70	60/192(31%)	33/180(18%)	13%	(4%,22%)
History of Dry Eye: N	75/302(25%)	44/296(15%)	10%	(4%,16%)
History of Dry Eye: Y	23/70(33%)	12/75(16%)	17%	(3%,31%)
Race: ASIAN	4/43(9%)	5/45(11%)	-2%	(-14%,11%)
Race: BLACK	12/45(27%)	7/38(18%)	8%	(-10%,26%)
Race: WHITE	82/284(29%)	44/288(15%)	14%	(7%,20%)
Day 1 ACC+ACF>=3: N	24/67(36%)	19/96(20%)	16%	(2%,30%)
Day 1 ACC+ACF>=3: Y	74/305(24%)	37/275(13%)	11%	(5%,17%)
Iris Color: BLUE	28/86(33%)	12/85(14%)	18%	(6%,31%)
Iris Color: BROWN	53/215(25%)	34/217(16%)	9%	(1%,17%)
Iris Color: GREEN	4/17(24%)	3/28(11%)	13%	(-10%,36%)
Iris Color: HAZEL	13/51(25%)	6/40(15%)	10%	(-6%,27%)
Iris Color: OTHER	0/3(0%)	1/1(100%)	-100%	(-100%,-100%)

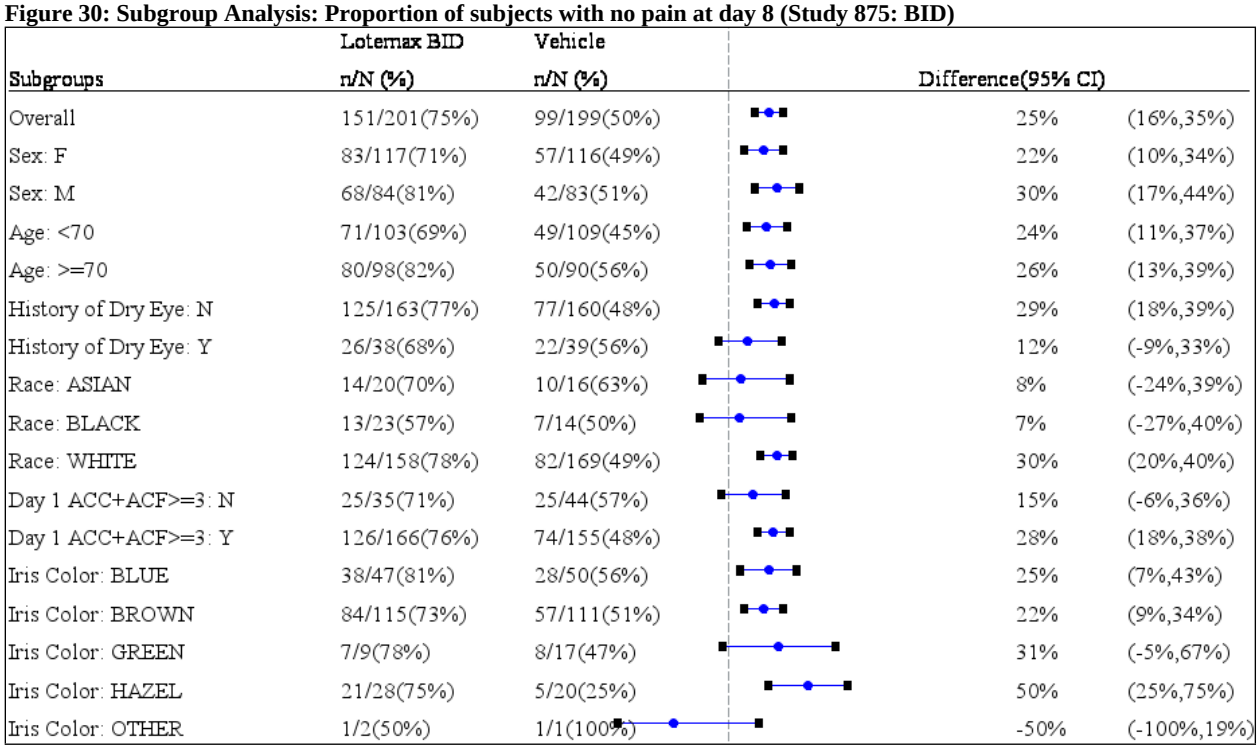
Source: Reviewer's Analysis. Subjects who received rescue therapy and those with missing data are treated as treatment failures

Figure 29: Subgroup Analysis: Proportion of subjects with no pain at day 8 (Study 842: BID)

Subgroups	Lotemax BID n/N (%)	Vehicle n/N (%)	Difference(95% CI)	
Overall	126/171(74%)	82/172(48%)	26%	(16%,36%)
Sex: F	71/94(76%)	46/100(46%)	30%	(16%,43%)
Sex: M	55/77(71%)	36/72(50%)	21%	(6%,37%)
Age: <70	51/77(66%)	36/82(44%)	22%	(7%,37%)
Age: >=70	75/94(80%)	46/90(51%)	29%	(16%,42%)
History of Dry Eye: N	103/139(74%)	63/136(46%)	28%	(17%,39%)
History of Dry Eye: Y	23/32(72%)	19/36(53%)	19%	(-3%,42%)
Race: ASIAN	19/23(83%)	13/29(45%)	38%	(14%,62%)
Race: BLACK	12/22(55%)	10/24(42%)	13%	(-16%,42%)
Race: WHITE	95/126(75%)	59/119(50%)	26%	(14%,38%)
Day 1 ACC+ACF>=3: N	24/32(75%)	24/52(46%)	29%	(9%,49%)
Day 1 ACC+ACF>=3: Y	102/139(73%)	58/120(48%)	25%	(13%,37%)
Iris Color: BLUE	32/39(82%)	18/35(51%)	31%	(10%,51%)
Iris Color: BROWN	71/100(71%)	49/106(46%)	25%	(12%,38%)
Iris Color: GREEN	3/8(38%)	4/11(36%)	1%	(-43%,45%)
Iris Color: HAZEL	20/23(87%)	11/20(55%)	32%	(6%,58%)

Source: Adapted from Table 14.2.1.5 of the study reports and Table AHT1-AHT4 submitted as a response to information request. Subjects who received rescue therapy and those with missing data are treated as treatment failures

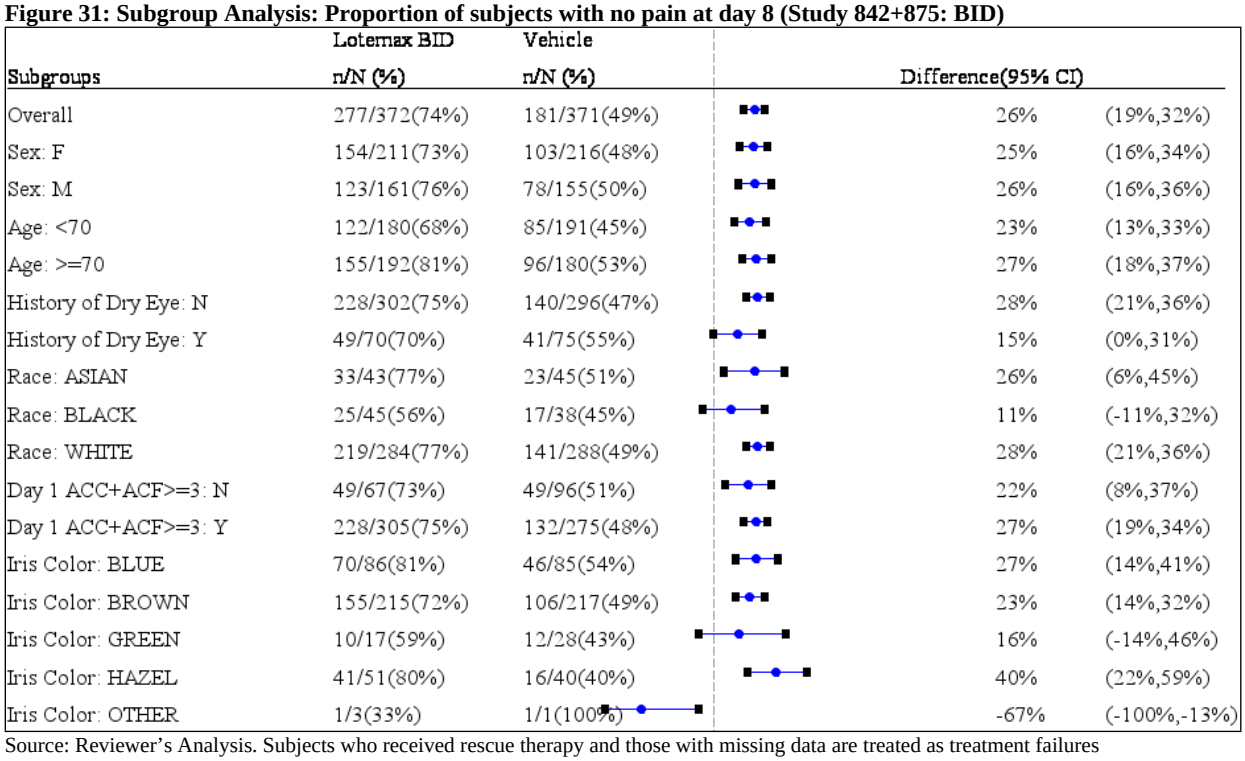
Figure 30: Subgroup Analysis: Proportion of subjects with no pain at day 8 (Study 875: BID)



Subgroups	Lotemax BID n/N (%)	Vehicle n/N (%)	Difference(95% CI)	
Overall	151/201(75%)	99/199(50%)	25%	(16%,35%)
Sex: F	83/117(71%)	57/116(49%)	22%	(10%,34%)
Sex: M	68/84(81%)	42/83(51%)	30%	(17%,44%)
Age: <70	71/103(69%)	49/109(45%)	24%	(11%,37%)
Age: >=70	80/98(82%)	50/90(56%)	26%	(13%,39%)
History of Dry Eye: N	125/163(77%)	77/160(48%)	29%	(18%,39%)
History of Dry Eye: Y	26/38(68%)	22/39(56%)	12%	(-9%,33%)
Race: ASIAN	14/20(70%)	10/16(63%)	8%	(-24%,39%)
Race: BLACK	13/23(57%)	7/14(50%)	7%	(-27%,40%)
Race: WHITE	124/158(78%)	82/169(49%)	30%	(20%,40%)
Day 1 ACC+ACF>=3: N	25/35(71%)	25/44(57%)	15%	(-6%,36%)
Day 1 ACC+ACF>=3: Y	126/166(76%)	74/155(48%)	28%	(18%,38%)
Iris Color: BLUE	38/47(81%)	28/50(56%)	25%	(7%,43%)
Iris Color: BROWN	84/115(73%)	57/111(51%)	22%	(9%,34%)
Iris Color: GREEN	7/9(78%)	8/17(47%)	31%	(-5%,67%)
Iris Color: HAZEL	21/28(75%)	5/20(25%)	50%	(25%,75%)
Iris Color: OTHER	1/2(50%)	1/1(100%)	-50%	(-100%,19%)

Source: Adapted from Table 14.2.1.5 of the study reports and Table AHT1-AHT4 submitted as a response to information request. Subjects who received rescue therapy and those with missing data are treated as treatment failures

Figure 31: Subgroup Analysis: Proportion of subjects with no pain at day 8 (Study 842+875: BID)



Subgroups	Lotemax BID n/N (%)	Vehicle n/N (%)	Difference(95% CI)	
Overall	277/372(74%)	181/371(49%)	26%	(19%,32%)
Sex: F	154/211(73%)	103/216(48%)	25%	(16%,34%)
Sex: M	123/161(76%)	78/155(50%)	26%	(16%,36%)
Age: <70	122/180(68%)	85/191(45%)	23%	(13%,33%)
Age: >=70	155/192(81%)	96/180(53%)	27%	(18%,37%)
History of Dry Eye: N	228/302(75%)	140/296(47%)	28%	(21%,36%)
History of Dry Eye: Y	49/70(70%)	41/75(55%)	15%	(0%,31%)
Race: ASIAN	33/43(77%)	23/45(51%)	26%	(6%,45%)
Race: BLACK	25/45(56%)	17/38(45%)	11%	(-11%,32%)
Race: WHITE	219/284(77%)	141/288(49%)	28%	(21%,36%)
Day 1 ACC+ACF>=3: N	49/67(73%)	49/96(51%)	22%	(8%,37%)
Day 1 ACC+ACF>=3: Y	228/305(75%)	132/275(48%)	27%	(19%,34%)
Iris Color: BLUE	70/86(81%)	46/85(54%)	27%	(14%,41%)
Iris Color: BROWN	155/215(72%)	106/217(49%)	23%	(14%,32%)
Iris Color: GREEN	10/17(59%)	12/28(43%)	16%	(-14%,46%)
Iris Color: HAZEL	41/51(80%)	16/40(40%)	40%	(22%,59%)
Iris Color: OTHER	1/3(33%)	1/1(100%)	-67%	(-100%,-13%)

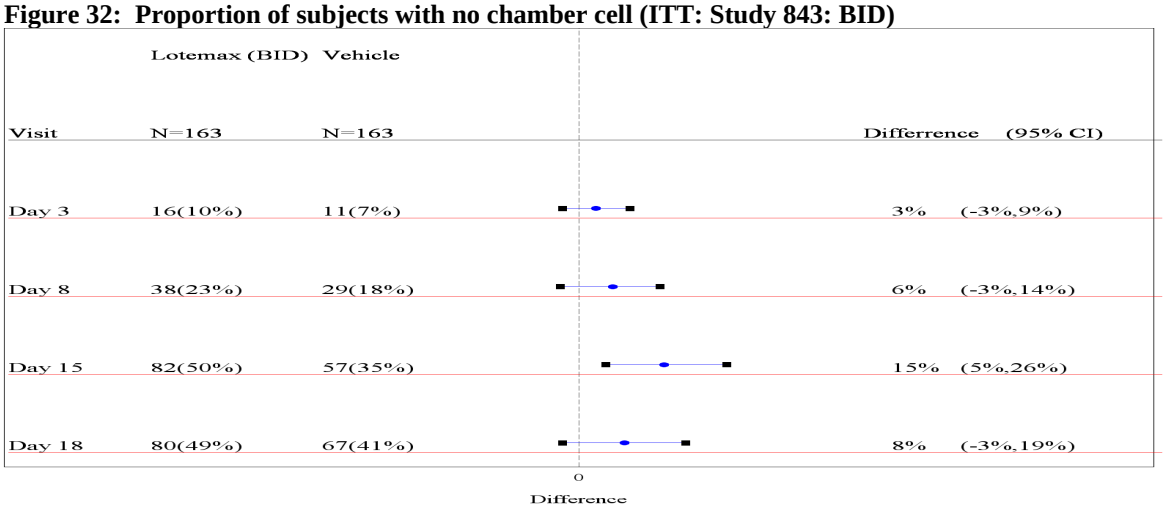
Source: Reviewer's Analysis. Subjects who received rescue therapy and those with missing data are treated as treatment failures

7.2 Summary of Study 843

Study 843 was a multi-center, randomized, double-masked, parallel-group, vehicle-controlled study. In this study, 326 subjects were randomized in a 1:1 ratio to LE gel 0.38% BID or vehicle. Treatment duration for this study was approximately 14 days. The proportion of subjects with complete resolution of AC cells (cell score = 0) in the study eye at postoperative Day 8 and the proportion of subjects with complete resolution of pain in the study eye at postoperative Day 8 were the two efficacy endpoints. The primary efficacy analysis compared the LE gel 0.38% BID against vehicle with respect to these two endpoints using a Pearson's chi-square-test. A 95% confidence interval (CI) was constructed around the treatment difference using asymptotic normal approximations. The primary efficacy analysis was conducted using all randomized subjects (ITT population) with missing data imputed as treatment failures. Besides, subjects placed on rescue medication prior to the visit being summarized were also considered failures. Supportive analyses of the primary analysis were repeated on the per-protocol population and on the ITT population imputing missing values and post-rescue values using the LOCF method.

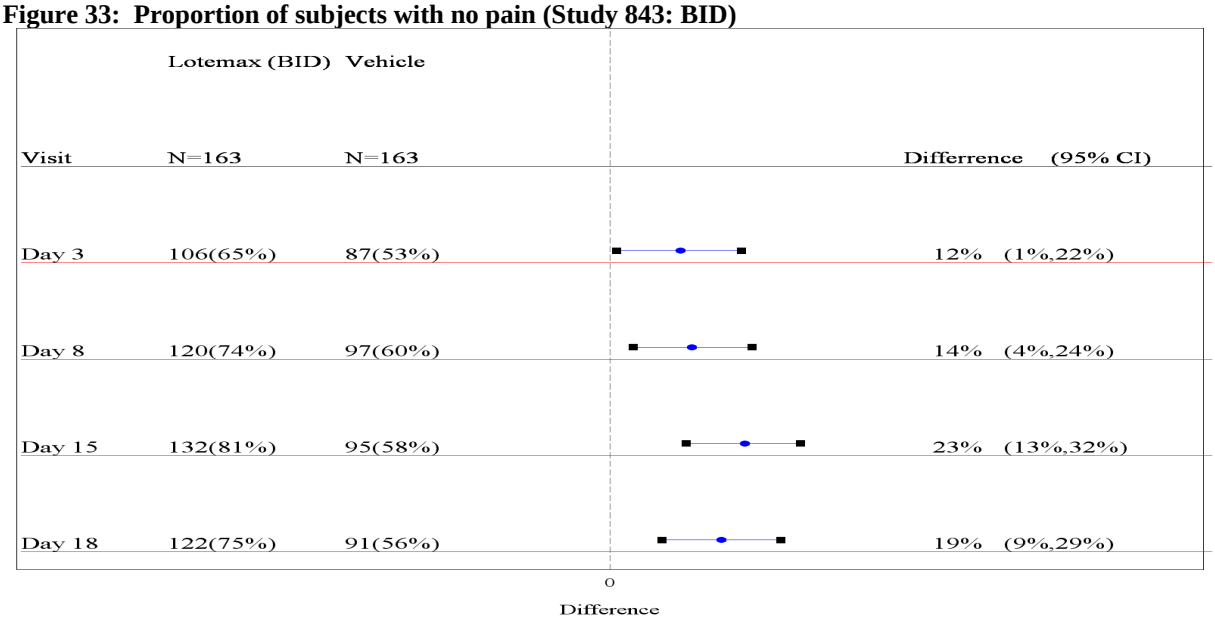
A sequential testing procedure was used to control the overall type I error rate at 5%. The hypotheses for pain was to be tested only if the hypothesis for complete resolution of AC cells in the study eye was rejected at 2-sided alpha = 0.05. The efficacy summary results are presented in Figure 32-Figure 35. The proportion of subjects with complete resolution of AC cells in the study eye (cell score = 0) at Day 8 was higher in the LE gel 0.38% BID group (23.3%; 38/163) compared to the vehicle group (17.8%; 29/163). The 5.5% treatment difference however was not statistically significant (95% CI: -3.2%, 14.3%). Consequently, because of the pre-specified hierarchical testing procedure, no formal hypothesis testing could be conducted for the pain outcome Therefore, the criteria for success was not fulfilled for this study.

Figure 32: Proportion of subjects with no chamber cell (ITT: Study 843: BID)



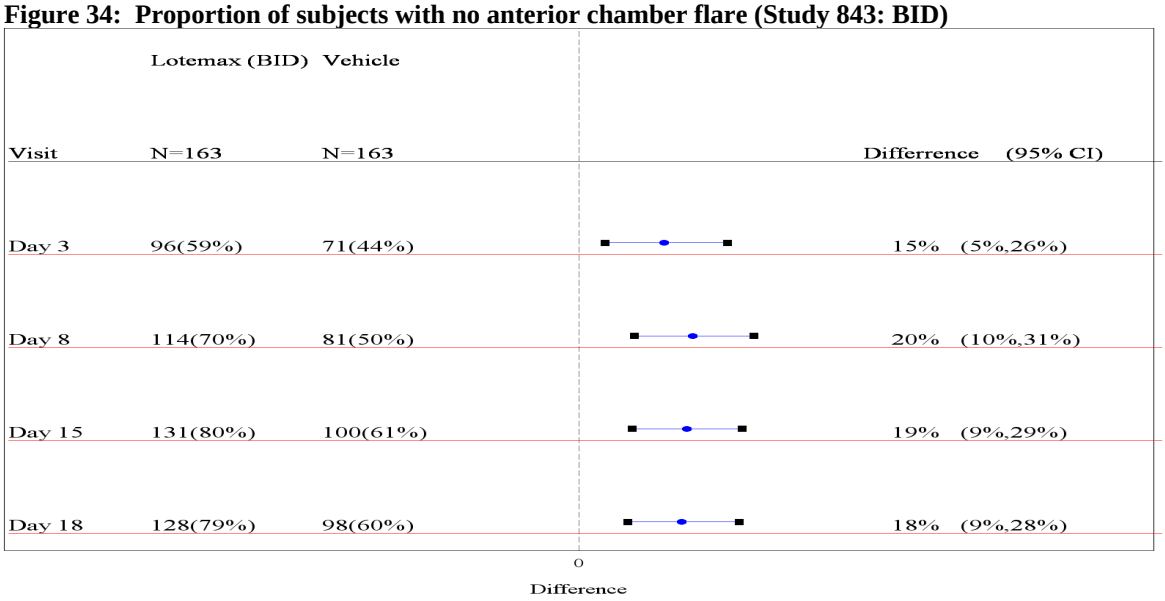
Source: Table 14.2.2.1.2 of the study report. Subjects who received rescue medication prior to the evaluation of efficacy and subjects with missing anterior chamber cells outcome were treated as treatment failures.

Figure 33: Proportion of subjects with no pain (Study 843: BID)



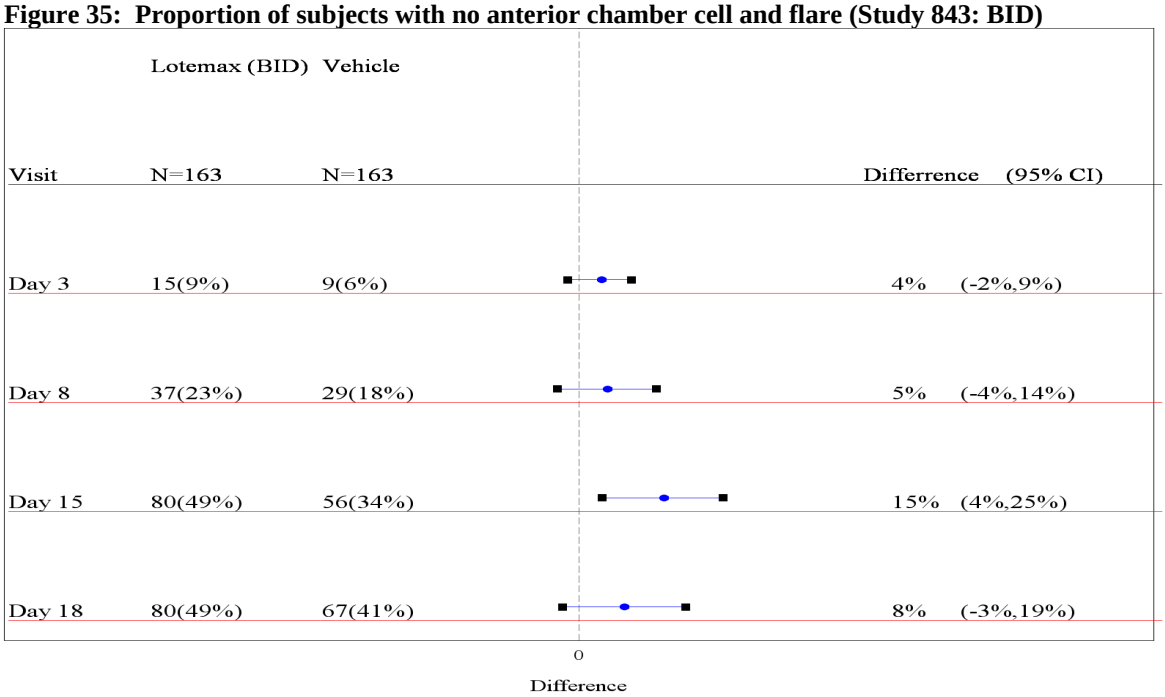
Source: Table 14.2.3.1.2 of the study report. Subjects who received rescue medication prior to the evaluation of efficacy and subjects with missing pain outcome were treated as treatment failures.

Figure 34: Proportion of subjects with no anterior chamber flare (Study 843: BID)



Source: Table 14.2.4.1.2 of the study report. Subjects who received rescue medication prior to the evaluation of efficacy and subjects with missing pain outcome were treated as treatment failures.

Figure 35: Proportion of subjects with no anterior chamber cell and flare (Study 843: BID)



Source: Table 14.2.6.1.2 of the study report. Subjects who received rescue medication prior to the evaluation of efficacy and subjects with missing pain outcome were treated as treatment failures.

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/s/

ABEL T ESHETE
01/24/2019 01:47:37 PM

YAN WANG
01/24/2019 02:03:32 PM
I concur.