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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA022212
Supplement #:	SUPPL-11
Drug Name:	Durezol (difluprednate ophthalmic emulsion 0.05%)
Indication(s):	Treatment of inflammation following cataract surgery in a Pediatric population 0 to 3 years of age.
Applicant:	Alcon Pharmaceuticals
Date(s):	Stamp Date: September 25, 2012 PDUFA date: March 25, 2013
Review Priority:	Priority Review
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Keywords: anterior cell grade, global assessment score of postoperative inflammation, cataract surgery.

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1 EXECUTIVE SUMMARY

This NDA supplement was submitted in response to the Agency's request for pediatric information on Durezol (difluprednate ophthalmic emulsion 0.05%). Difluprednate ophthalmic emulsion 0.05% (Durezol) was approved by the FDA (NDA 22212) for use in adults for the treatment of inflammation and pain associated with ocular surgery on June 23, 2008. At the time of approval, the pediatric study was indicated as a post-marketing commitment.

In support for this NDA supplement, the applicant conducted a phase 3B, multicenter, randomized, double-masked, parallel-group, active-controlled study designed to assess the safety and efficacy of Difluprednate Ophthalmic Emulsion, 0.05% (Durezol™) dosed 4 times daily (QID) compared to Prednisolone Acetate Ophthalmic Suspension, 1% (Pred Forte™) dosed QID for the treatment of inflammation following cataract surgery in a pediatric population 0 to 3 years of age.

A total of 80 subjects were randomized equally to receive either Durezol or Pred Forte. The primary efficacy endpoint was the number and percentage of patients with an anterior cell grade of 0 (no cells) on Day 15 ± 2 days. The key secondary endpoints were a global assessment score of postoperative inflammation and the corresponding individual components of the global assessment score at each postoperative visit.

The primary efficacy analysis was a summary by treatment group of the number and percentage of patients with an anterior cell grade of 0 (no cells) on Day 15 ± 2 days. The study was not powered to detect a significant difference between the two treatments and no inferential analysis was planned and conducted. The intent-to-treat (ITT) population defined as all patients who received at least one administration of study drug was used as the main analysis population. The Last Observation Carried Forward (LOCF) approach was used for imputing missing data for all efficacy endpoints. The Per-Protocol (PP) population which consisted of patients in the ITT population who had no major protocol violations such as violation of entry criteria, noncompliance and the use of prohibited medications was also considered. No data imputation was done for the analysis involving the PP population.

The primary analysis results using the ITT population and the corresponding PP analysis for the primary endpoint and the key secondary endpoint are presented in Table 1. Based on the ITT analysis, the percentage of patients with an anterior cell grade of 0 (no cells) on Day 15 ± 2 days for patients treated with Durezol and Pred Forte were 78.9% and 77.5%, respectively. The percentage of patients with a global assessment score of postoperative inflammation of zero at Day 15 ± 2 for patients treated with Durezol and patients treated with Pred Forte were 56.4% and 50.0%, respectively.

The safety population consisted of 79 subjects (39 and 40 in the Durezol and Pred Forte groups respectively). There were no deaths and other significant adverse events reported during the study.

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Table 1: Results for the Primary and Key Secondary Endpoints

	Percentage of Subjects with Anterior Cell Grade of 0 on Day 15		
Population	**Durezol**	**Pred Forte**	**% Difference (95% CI)**
ITT	30/38* (78.9%)	31/40 (77.5%)	1.4 (-16.9, 19.8)
PP	26/33 (78.8%)	23/30 (76.7%)	2.1 (-18.5, 22.7)
	Percentage of Subjects with a Global Assessment of Inflammation Score of zero on Day 15		
ITT	22/39 (56.4%)	20/40 (50.0%)	6.4 (-15.6, 28.4%)
PP	19/34 (55.9%)	15/33 (45.5%)	10.4 (-13.4, 34.2)

Source: Updated efficacy table submitted by the applicant. LOCF was used to impute missing values for the ITT analysis. *Note: One subject in the Durezol group did not have any measurement at all time points for the primary efficacy endpoint and hence was excluded from the analysis. The subject however had measures for the components of the Global assessment score.

In this NDA, the applicant proposed a revised drug labeling based on safety data from this Phase 3b study. The major changes were made to the Adverse Reactions (6.1) and Pediatric Use (8.4) sections of the label. The revisions are in agreement with the results of the safety data from this NDA. No efficacy data from this Phase 3b study was included in the proposed drug labeling. This reviewer does not have any issues with the proposed revised drug labeling.

2 INTRODUCTION

The applicant performed a supplemental pediatric study as part of a post-marketing commitment in support of their NDA for Durezol (difluprednate ophthalmic emulsion 0.05%) which was approved for the treatment of inflammation following cataract surgery on June 23, 2008. At the time of approval, the pediatric study was indicated as a post-marketing commitment.

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 study reviewed.

2.1.1 Drug Class and Indication

Difluprednate is a synthetic (b) (4) derivative first developed by (b) (4) Difluprednate was first developed as a dermatological preparation (marketed in Japan under the product name Myser®), and subsequently was developed in Japan as an ophthalmic emulsion by (b) (4). On June 28, 2008, Durezol was approved by the FDA for the treatment of inflammation following cataract surgery in adults.

2.1.2 History of Drug Development

Durezol (difluprednate ophthalmic emulsion 0.05%) was approved for the treatment of inflammation following cataract surgery on June 23, 2008. At the time of approval, the pediatric study was indicated as a post-marketing commitment. The Agency issued a written request on 18 February 2009 for pediatric information on Durezol® (difluprednate ophthalmic emulsion 0.05%). The applicant submitted a pediatric trial protocol [Protocol ST-601-007] under IND 75,713 [SN0035] on 04 August 2009. An amendment [SN0040] to the IND for Alcon protocol C-10-004 [A Phase 3B, Multicenter, Randomized, Double-Masked, Parallel-Group, Active-Controlled Study of the Safety and Efficacy of Difluprednate Ophthalmic Emulsion, 0.05% (Durezol™) 4 Times Daily (QID) and Prednisolone Acetate Ophthalmic Suspension, 1.0% (Pred Forte™) QID for the Treatment of Inflammation Following Cataract Surgery in Children 0 to 3 Years of Age] on 01 June 2010.

The first patient was enrolled into the trial on 16 August 2010. With the Agency's agreement, the protocol was amended to allow for the use of contact lenses and the amended protocol was submitted to the IND [SN0051] on 03 March 2011. On 12 September 2011, the Agency granted an extension of the submission date of the study report from 01 October 2011 to 31 December 2012.

2.1.3 Study Reviewed

A phase 3B, multicenter, randomized, double-masked, parallel-group, active-controlled clinical trial was used to support the NDA supplement. The brief summary of this study is presented in Table 2. In this study subjects were randomly allocated to receive either Durezol or Pred Forte. A total of 80 subjects, all within the United States, were involved.

Table 2: Summary of Pivotal Studies Reviewed

Study number	Design	Treatment/Sample size	Endpoint/Analysis	Applicant's findings
C-10-004	A Phase 3B, Multicenter, Randomized, Double-Masked, Parallel-Group, Active-Controlled Study of the Safety and Efficacy of Difluprednate Ophthalmic Emulsion, 0.05% (Durezol™) 4 Times Daily (QID) and Prednisolone Acetate Ophthalmic Suspension, 1.0% (Pred Forte™) QID for the Treatment of Inflammation Following Cataract Surgery in Children 0 to 3 Years of Age	– Difluprednate Ophthalmic Emulsion, 0.05%; N=39 – Prednisolone Acetate Ophthalmic Suspension, 1.0%; N=40 Note: Parents or guardians instilled patients' assigned study medications once on the day of surgery (Day 0) and 4 times daily (QID) beginning on the day after surgery (Day 1) for 14 days followed by a tapering period of 14 days (dependent upon the Investigator's determination of adequate response to treatment). Patients were evaluated for safety and efficacy on the following visits: Day 0 (day of surgery), Day 1, Day 8 ± 1 day, Day 15 ± 2 days, and at the end of study drug treatment (Day 29 ± 2 days). Additional safety visits occurred at 1 week after the last dose of study drug (+ 2 days), and 3 months (+ 1 week), with the last visit occurring at the earliest on Day 92 + 1 week.	Primary: the primary efficacy endpoint was the number and percentage of patients with an anterior cell grade of 0 (no cells) on Day 15 ± 2 days. Key secondary: a global assessment score of postoperative inflammation and the corresponding individual components of the global assessment score at each postoperative visit (Day 1, Day 8 ± 1 day, Day 15 ± 2 days, Day 29 ± 2 days, 1 week after the last dose of study drug + 2 days, and 3 months + 1 week). The primary efficacy analysis was a summary by treatment group of the number and percentage of patients with an anterior cell grade of 0 (no cells) on Day 15 ± 2 days. No inferential analysis was planned or performed.	The percentage of patients with complete clearing of anterior chamber cells on Day 15 ± 2 days, following QID dosing for 14 days post cataract surgery, was similar for patients treated with difluprednate 0.05% (78.9%) and patients treated with prednisolone 1% (77.5%). The percentage of patients completely clear of postoperative inflammation (global assessment score = 0) on Day 15 ± 2 days was similar for patients treated with difluprednate 0.05% and patients treated with prednisolone acetate 1% (56.4% and 50%, respectively).

Source: Reviewer's summary.

2.2 Data Sources

The data sources for this review include the applicant's clinical study report and SAS datasets all submitted electronically. The datasets and the analysis programs are located at \\cdsesub1\evsprod\NDA022212\0085. Updated efficacy tables are located at \\cdsesub1\evsprod\NDA022212\0088.

3 STATISTICAL EVALUATION

This section provides a detailed review of the study considered in this review.

3.1 Data and Analysis Quality

The submitted data are generally of good quality. The reviewer was able to reproduce the primary analysis results from reported individual efficacy report data. The final and the amended protocols are all submitted. There was no need to get support from the Computational Science Center to conduct the analysis and reproduce the results of the applicant.

3.2 Evaluation of Efficacy

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

3.2.1 Study Design and Endpoints

The study is a phase 3B, multi-center, randomized, double-masked, active controlled study designed to investigate the safety and efficacy of Difluprednate Ophthalmic Emulsion, 0.05% in the treatment of Ocular Inflammation and Pain Associated with Cataract Surgery in pediatric population. A total of 80 subjects who met the inclusion/exclusion criteria were randomized to receive either Difluprednate Ophthalmic Emulsion, 0.05%; or Prednisolone Acetate Ophthalmic Suspension, 1.0%.

Patients were screened between Day -14 to Day -1 [+ 1 day], and informed consent was obtained from the patient's parent or legal guardian. Patients who met all eligibility criteria were randomized to treatment on Day 0 (day of surgery). Study drug was administered on Day 0. Safety and efficacy evaluations were conducted at study visits on Day 0 (day of surgery), Day 1, Day 8 ± 1 day, Day 15 ± 2 days, and for safety on Days 29 ± 2 days, 1 week after the last dose of study drug + 2 days, and 3 months + 1 week.

The primary objective of this study was to compare, in a pediatric population 0 to 3 years of age, the safety and efficacy of Durezol compared to Pred Forte for the treatment of inflammation following cataract surgery. The primary efficacy endpoint was the number and percentage of patients with an anterior cell grade of 0 (no cells) on Day 15 ± 2 days. The secondary efficacy endpoints were a global assessment score of postoperative inflammation and the corresponding individual components of the global assessment

score at each postoperative visit. The anterior cell and flare grades are summarized in Table 3.

Table 3: Summary Grades for Anterior Chamber Cells and Flare

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Anterior Chamber Cells	0 cells	1-10 cells	11-20 cells	21-50 cells	50+ cells
Anterior Chamber Flare	Absent	Mild	Moderate	Severe	

3.2.2 Methodologies

No inferential statistical analysis was planned and conducted. The primary efficacy analysis was a summary by treatment group of the number and percentage of patients with an anterior cell grade of 0 (no cells) on Day 15 ± 2 days. A confidence interval for treatment differences was constructed using the normal approximation method. The intent-to-treat (ITT) population defined as all patients who received at least one administration of study drug was used as the main analysis population. The Last Observation Carried Forward (LOCF) approach was used for imputing missing data for all efficacy endpoints. The Per-Protocol (PP) population which consists of subjects in the ITT population who had no major protocol violations such as violation of entry criteria, noncompliance, and the use of prohibited medications was also considered. No data imputation was done for the analysis involving the PP population.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Demographic and Baseline Characteristics

The mean age of subjects in this study was similar in both treatment groups. Both groups however had relatively higher variability in terms of the age of the patients (Table 4).

Table 4: Descriptive Statistics for Age (in Months) by Treatment (ITT)

Measure	Durezol (N=39)	Pred Forte (N=40)
Mean	12.3	12.4
SD	15.4	14.8
Median	4.0	5.0
(Min, Max)	(0, 47)	(0, 47)

Source: Table 11.2.-2 of the study report

In the Pred Forte group, the number of male and female patients was equal whereas there was slightly higher number of female patients in the Durezol group. The percentage of participants with brown eyes was higher than other colored eyes for both treatment groups. The majority of participants were white in both treatment groups (Table 5).

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Table 5: Demographic Profile of Subjects (ITT)

Characteristics	Durezol (N=39) n (%)	Pred Forte (N=40) n (%)
Age		
0-27 Days	3 (7.7)	3 (7.5)
28 Days- 23 Months	28 (71.8)	26 (65.0)
2-3 Years	8 (20.5)	11 (27.5)
Sex		
Male	17 (43.6)	20 (50.0)
Female	22 (56.4)	20 (50.0)
Ethnicity		
Hispanic, Latino, or Spanish	9 (23.1)	8 (20.0)
Not Hispanic, Latino, or Spanish	30 (76.9)	32 (80.0)
Race		
White	21 (53.8)	24 (53.8)
Black or African American	9 (23.1)	9 (23.1)
Asian	0 (0.0)	1 (0.0)
Multi-Racial	3 (7.7)	2 (7.7)
Other	6 (15.4)	4 (15.4)
Iris Color		
Brown	22 (56.4)	22 (55.0)
Green	0 (0.0)	1 (2.5)
Blue	15 (38.5)	16 (40.0)
Grey	1 (2.6)	0 (0.0)
Other	1 (2.6)	1 (2.5)

Source: Table 11.2.-1 of the study report

3.2.3.2 Patient Disposition

Of the 79 subjects included in the ITT population, none of the 39 subjects in the Durezol group and only 3(7.5%) of the 40 subjects in the Pred Forte group discontinued the study early. Two of the subjects discontinued based on the suggestion of the investigator and the other subject was lost- to follow up (Table 6 and Table 7).

Table 6: Summary of Study Completion (ITT)

	Total (N=79) n (%)	Durezol (N=39) n (%)	Pred Forte (N=40) n (%)
Completed Study	76 (96.2)	39 (100.0)	37 (92.5)
Discontinued	3 (3.8)	0 (0.0)	3 (7.5)

Source: Table 10.1.-1 of the study report

Table 7: Reasons for Study Discontinuation (ITT)

	Total (N=79) n (%)	Durezol (N=39) n (%)	Pred Forte (N=40) n (%)
Total	3 (3.8)	0 (0.0)	3 (7.5)
Lost to Follow-Up	1 (1.3)	0 (0.0)	1 (2.5)
Investigators Decision	2 (2.5)	0 (0.0)	2 (5.0)

Source: Table 10.1.-6 of the study report

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3.2.3.1 Efficacy Results

The percentage of patients with complete clearing of anterior chamber cells on Day 15 ± 2 days, in the Durezol and Pred Forte groups were 78.9% and 77.5%, respectively.

Table 8: Percentage of Patients with Anterior Cell Grade of 0 by Visit (ITT)

Visit	Durezol (N=39) n (%)	Pred Forte (N=40) n (%)	Difference in Percentage (95% CI)
Day 1	9 (23.7)	16 (40.0)	-16.3 (-36.6, 4.0)
Day 8	21 (55.3)	23 (57.5)	-2.2 (-24.3, 19.8)
Day 15	30 (78.9)	31 (77.5)	1.4 (-16.9, 19.8)
Day 29	34 (89.5)	38 (95.0)	-5.5 (-17.4, 6.3)
1 Week after last Dose	37 (97.4)	38 (95.0)	2.4 (-6.1, 10.8)
3 Months	36 (94.7)	39 (97.5)	-2.8 (-11.4, 5.8)

Source: Applicant's updated efficacy table. LOCF was used to impute missing values.

Table 9: Descriptive Summary of Anterior Cell Grade by Visit (ITT)

Visit		Durezol (N=39) n (%)	Pred Forte (N=40) n (%)	Treatment Difference in Mean (95% CI)
Screening	Mean (SD)	0.0 (0.00)	0.0 (0.00)	NA
	Median	0	0	
	(Min, Max)	(0, 0)	(0, 0)	
Day 1	Mean (SD)	1.0 (0.72)	1.0 (0.96)	0.0 (-0.4, 0.4)
	Median	1	1	
	(Min, Max)	(0, 3)	(0, 4)	
Day 8	Mean (SD)	0.6 (0.72)	0.5 (0.68)	0.0 (-0.3, 0.3)
	Median	0	0	
	(Min, Max)	(0, 3)	(0, 2)	
Day 15	Mean (SD)	0.3 (0.60)	0.3 (0.55)	0.0 (-0.3, 0.2)
	Median	0	0	
	(Min, Max)	(0, 3)	(0, 2)	
Day 29	Mean (SD)	0.1 (0.31)	0.1 (0.35)	0.0 (-0.1, 0.2)
	Median	0	0	
	(Min, Max)	(0, 1)	(0, 2)	
1 week after Last Dose	Mean (SD)	0.0 (0.16)	0.1 (0.35)	0.0(-0.2, 0.1)
	Median	0	0	
	(Min, Max)	(0, 1)	(0, 2)	
3 Months	Mean (SD)	0.1 (0.23)	0.1 (0.32)	0.0 (-0.1, 0.1)
	Median	0	0	
	(Min, Max)	(0, 1)	(0, 2)	

Source: Applicant's updated efficacy table.

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The key secondary endpoints were the proportions of subjects who had clear inflammation as measured by the Global Assessment of Inflammation score and its individual components. The individual components of the global assessment score included anterior chamber cell grade, anterior chamber flare grade, corneal clarity, wound integrity, conjunctival injection, ciliary/limbal injection, chemosis, hypopyon, vitritis, photophobia and lacrimation. The Global Assessment score had three grade levels (0= "Clear", 1= "improving satisfactorily" and 2="not improving or worsening"). The 4 point assessment scale of the individual components is presented in Table 10.

The proportion of subjects with Global Assessment of Inflammation score of zero (clear) on Day 15 ± 2 days were 50.0% and 56.4%, for the Durezol and Pred Forte groups respectively (Table 11).

The proportions of subjects with a score of zero (absent) in the individual components of the global assessment score for the ITT population are given in Table 12--Table 21. On day 15, the percentage of patients with a score of zero in the individual components of the Global assessment score ranged between 74% and 100% in the Durezol group and between 70.5% and 100% in the Pred Forte group. The smallest percentage was observed for flare for both groups. The Durezol group had higher observed percentage of subjects with a score of zero compared to the Pred Forte group in all components except in Conjunctival Injection on Day 15.

Table 10: Global Assessment of Inflammation – Individual Component Scoring Categories

	Component	Measurement Scale
Signs	Anterior Chamber Cell Grade	0=0 cells, 1=1-10 cells, 2=11-20 cells, 3=21-50 cells, 4= 50+ cells
	Anterior Chamber Flare Grade	0=Absent , 1=mild, 2=Moderate, 3= severe
	Corneal Clarity	0=Absent , 1=mild, 2=Moderate, 3= severe*
	Conjunctival Injection	0=Absent , 1=mild, 2=Moderate, 3= severe
	Ciliary/ Limbal Injection	0=Absent , 1=mild, 2=Moderate, 3= severe*
	Chemosis	0=Absent , 1=mild, 2=Moderate, 3= severe*
	Hypopyon	0=Absent , 1=mild, 2=Moderate, 3= severe*
	Vitritis	0=Absent , 1=mild, 2=Moderate, 3= severe*
	Wound Integrity	0=Absent , 1=mild, 2=Moderate, 3= severe*
	Cataract	0=Absent , 1=mild, 2=Moderate, 3= severe*
Symptoms	Photophobia	0=Absent , 1=mild, 2=Moderate, 3= severe*
	Lacrimation	0=Absent , 1=mild, 2=Moderate, 3= severe*

Source: Table 9.5.1.1.-1 of the study report.
* Severe as determined by the investigator

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Table 11: Percentage of Patients with a Score of 0 ("Clear") on Global Assessment of Inflammation by Visit (ITT)

Visit	Durezol (N=39) n (%)	Pred Forte (N=40) n (%)	Difference in Percentage (95% CI)
Day 1	12 (30.8)	7 (17.5)	13.3 (-5.4, 31.9)
Day 8	19 (48.7)	10 (25.0)	23.7 (3.1, 44.4)
Day 15	22 (56.4)	20 (50.0)	6.4 (-15.6, 28.4)
Day 29	31 (79.5)	29 (72.5)	7.0 (-11.8, 25.8)
1 Week after last Dose	35 (89.7)	36 (90.0)	-0.3 (-13.6, 13.1)
3 Months	36 (92.3)	37 (92.5)	-0.2 (-11.9, 11.5)

Source: Table 3 of the updated efficacy results submitted by the applicant

Table 12: Percentage of Patients with a Score of 0 ("Absent") on Flare by Visit (ITT)

Visit	Durezol (N=39) n (%)	Pred Forte (N=40) n (%)	Difference in Percentage (95% CI)
Screening	36 (94.7)	38 (95.0)	-0.3 (-10.1, 9.5)
Day 1	16 (41.0)	18 (45.0)	-4.0 (-25.8, 17.8)
Day 8	24 (61.5)	21 (52.5)	9.0 (-12.7, 30.8)
Day 15	29 (74.4)	28 (70.0)	4.4 (-15.4, 24.1)
Day 29	34 (87.2)	37 (92.5)	-5.3 (-18.6, 8.0)
1 Week after last Dose	37 (94.9)	37 (92.5)	2.4 (-8.3, 13.1)
3 Months	36 (92.3)	38(95.0)	-2.7(-13.4, 8.1)

Source: Table 4 of the updated efficacy results submitted by the applicant.

Table 13: Percentage of Patients with a Score of 0 ("Absent") on Corneal Clarity by Visit (ITT)

Visit	Durezol (N=39) n (%)	Pred Forte (N=40) n (%)	Difference in Percentage (95% CI)
Screening	39 (100.0)	39 (97.5)	2.5(-2.3, 7.3)
Day 1	36 (92.3)	35 (87.5)	4.8 (-8.4, 18.0)
Day 8	37 (94.9)	36 (90.0)	4.9 (-6.7, 16.5)
Day 15	37 (94.9)	36 (90.0)	4.9 (-6.7, 16.5)
Day 29	38 (97.4)	39 (97.5)	-0.1 (-7.0, 6.9)
1 Week after last Dose	39 (100.0)	39 (97.5)	2.5 (-2.3, 7.3)
3 Months	39 (100.0)	39 (97.5)	2.5 (-2.3, 7.3)

Source: Table 5 of the updated efficacy results submitted by the applicant.

Table 14: Percentage of Patients with a Score of 0 ("Absent") on Conjunctival Injection by Visit (ITT)

Visit	Durezol (N=39) n (%)	Pred Forte (N=40) n (%)	Difference in Percentage (95% CI)
Screening	39 (100.0)	40 (100.0)	NA
Day 1	18 (46.2)	10 (25.0)	21.2 (0.5, 41.8)
Day 8	31 (79.5)	31 (77.5)	2.0 (-16.1, 20.1)
Day 15	35 (89.7)	37 (92.5)	-2.8 (-15.3, 9.8)

Day 29	38 (97.4)	38 (95.0)	2.4 (-5.9, 10.8)
1 Week after last Dose	39 (100.0)	40 (100.0)	0.0 (-,-)
3 Months	39 (100.0)	40 (100.0)	0.0 (-,-)

Source: Table 6 of the updated efficacy results submitted by the applicant

Table 15: Percentage of Patients with a Score of 0 ("Absent") on Ciliary/Limbal Injection by Visit (ITT)

Visit	Durezol (N=39) n (%)	Pred Forte (N=40) n (%)	Difference in Percentage (95% CI)
Screening	39 (100.0)	40 (100.0)	NA
Day 1	27 (69.2)	23 (57.5)	11.7 (-9.4, 32.8)
Day 8	35 (89.7)	36 (90.0)	-0.3 (-13.6,13.1)
Day 15	39 (100.0)	40 (100.0)	-2.8 (-15.3, 9.8)
Day 29	39 (100.0)	39 (97.5)	2.4 (-5.9, 10.8)
1 Week after last Dose	39 (100.0)	40 (100.0)	0.0 (-,-)
3 Months	39 (100.0)	40 (100.0)	0.0 (-,-)

Source: Table 7 of the updated efficacy results submitted by the applicant

Table 16: Percentage of Patients with a Score of 0 ("Absent") on Chemosis by Visit (ITT)

Visit	Durezol (N=39) n (%)	Pred Forte (N=40) n (%)	Difference in Percentage (95% CI)
Screening	39 (100.0)	40 (100.0)	NA
Day 1	32 (82.1)	34 (85.0)	-2.9 (-19.3, 13.4)
Day 8	38 (97.4)	40 (100.0)	-2.6 (-7.5, 2.4)
Day 15	39 (100.0)	39 (97.5)	-2.5 (-2.3, 7.3)
Day 29	39 (100.0)	40 (100.0)	0.0 (-,-)
1 Week after last Dose	39 (100.0)	40 (100.0)	0.0 (-,-)
3 Months	39 (100.0)	40 (100.0)	0.0 (-,-)

Source: Table 8 of the updated efficacy results submitted by the applicant

Table 17: Percentage of Patients with a Score of 0 ("Absent") on Hypopyon by Visit (ITT)

Visit	Durezol (N=39) n (%)	Pred Forte (N=40) n (%)	Difference in Percentage (95% CI)
Screening	39 (100.0)	40 (100.0)	NA
Day 1	39 (100.0)	40 (100.0)	0.0 (-,-)
Day 8	39 (100.0)	40 (100.0)	0.0 (-,-)
Day 15	39 (100.0)	40 (100.0)	0.0 (-,-)
Day 29	39 (100.0)	40 (100.0)	0.0 (-,-)
1 Week after last Dose	39 (100.0)	40 (100.0)	0.0 (-,-)
3 Months	39 (100.0)	40 (100.0)	0.0 (-,-)

Source: Table 9 of the updated efficacy results submitted by the applicant

Table 18: Percentage of Patients with a Score of 0 ("Absent") on Vitritis by Visit (ITT)

Visit	Durezol (N=39) n (%)	Pred Forte (N=40) n (%)	Difference in Percentage (95% CI)
Day 1	39 (100.0)	39 (97.5)	-2.5 (-2.3, 7.3)

Day 8	39 (100.0)	39 (97.5)	-2.5 (-2.3, 7.3)
Day 15	39 (100.0)	39 (97.5)	-2.5 (-2.3, 7.3)
Day 29	39 (100.0)	39 (97.5)	-2.5 (-2.3, 7.3)
1 Week after last Dose	39 (100.0)	39 (97.5)	-2.5 (-2.3, 7.3)
3 Months	39 (100.0)	39 (97.5)	-2.5 (-2.3, 7.3)

Source: Table 10 of the updated efficacy results submitted by the applicant

Table 19: Percentage of Patients with a Score of 0 ("Absent") on Wound Integrity by Visit (ITT)

Visit	Durezol (N=39) n (%)	Pred Forte (N=40) n (%)	Difference in Percentage (95% CI)
Day 1	39 (100.0)	40 (100.0)	0.0 (-,-)
Day 8	39 (100.0)	40 (100.0)	0.0 (-,-)
Day 15	39 (100.0)	40 (100.0)	0.0 (-,-)
Day 29	39 (100.0)	40 (100.0)	0.0 (-,-)
1 Week after last Dose	39 (100.0)	40 (100.0)	0.0 (-,-)
3 Months	39 (100.0)	40 (100.0)	0.0 (-,-)

Source: Table 12 of the updated efficacy results submitted by the applicant

Table 20: Percentage of Patients with a Score of 0 ("Absent") on Lacrimation by Visit (ITT)

Visit	Durezol (N=39) n (%)	Pred Forte (N=40) n (%)	Difference in Percentage (95% CI)
Screening	39 (100.0)	38 (95.0)	5.0 (-1.8, 11.8)
Day 1	25 (64.1)	29 (72.5)	-8.4 (-28.8, 12.1)
Day 8	37 (94.9)	39 (97.5)	-2.6 (-11.1,5.8)
Day 15	39 (100.0)	38 (95.0)	5.0 (-1.8, 11.8)
Day 29	39 (100.0)	40 (100.0)	0.0 (-,-)
1 Week after last Dose	39 (100.0)	40 (100.0)	0.0 (-,-)
3 Months	39 (100.0)	40 (100.0)	0.0 (-,-)

Source: Table 13 of the updated efficacy results submitted by the applicant

Table 21: Percentage of Patients with a Score of 0 ("Absent") on Photophobia by Visit (ITT)

Visit	Durezol (N=39) n (%)	Pred Forte (N=40) n (%)	Difference in Percentage (95% CI)
Screening	39 (100.0)	38 (95.0)	-0.1 (-7.0, 6.9)
Day 1	25 (64.1)	29 (72.5)	11.8 (-8.9, 32.5)
Day 8	37 (94.9)	39 (97.5)	2.2 (-11.7, 16.2)
Day 15	39 (100.0)	38 (95.0)	2.4 (-5.9, 10.8)
Day 29	39 (100.0)	40 (100.0)	4.9 (-4.6,14.5)
1 Week after last Dose	39 (100.0)	40 (100.0)	-2.5 (-2.3, 7.3)
3 Months	39 (100.0)	40 (100.0)	0.0 (-,-)

Source: Table 14 of the updated efficacy results submitted by the applicant

3.3 Evaluation of Safety

The safety population for this study consisted of 79 subjects; 39 in the Durezol group and 40 in the Pred Forte group. Safety assessments included Increased Ocular Pressure (IOP) assessment, visual acuity (VA), fundoscopic exam, collection of Adverse Events (AEs), observation of postoperative bacterial or fungal infection, and ocular signs. No deaths and no significant adverse events that lead to discontinuation were reported in this study. A total of 8 (20.5%) and 11 (27.5%) subjects experienced a non-fatal serious adverse event in the Durezol group and the Pred Forte group respectively. Except one in the Durezol group, the rest of the serious adverse events were not related to the treatment. A total of 29 (74.4%) subjects in the Durezol group and 30 (75.0%) subjects in the Pred Forte group experienced treatment emergent adverse events. The most common treatment emergent adverse event was medical observation which was experienced by 6 (15.4%) and 10(25.5%) subjects in the Durezol group and the Pred Forte group respectively. Five (12.8%) subjects in the Durezol group reported Nasopharyngitis compared to 2 (5.0%) in the Pred Forte group. Treatment related increase in IOP was reported in 2 (5.1%) subjects in the Durezol group and 1 (2.5%) subjects in the Pred Forte group (Table 22).

Table 22: Summary of Adverse events (AE)

Adverse Event Category	Durezol (N=39) n (%)	Pred Forte (N=40) n (%)
Deaths	0 (0.0)	0 (0.0)
Patients experiencing non-fatal AEs	8 (20.5)	11 (27.5)
Treatment Related	1 (2.6)	0 (0.0)
Not Related to Treatment	7 (17.9)	11 (27.5)
Patients discontinued due to AEs	0 (0.0)	0 (0.0)
Patients with at least one treatment emergent AE (related and not related combined)		
Treatment-emergent AE reported in 2or more patients		
Conjunctivitis	3 (7.7)	0 (0.0)
Posterior capsule opacification	3 (7.7)	0 (0.0)
Eye inflammation	0 (0.0)	2 (5.0)
Pyrexia	0 (0.0)	2 (5.0)
Nasopharyngitis	5 (12.8)	2 (5.0)
Ear infection	3 (7.7)	1 (2.5)
Sinusitis	2 (5.1)	0 (0.0)
Medical observation	6 (15.4)	10 (25.0)
Intraocular pressure increased	3 (7.7)	1 (2.5)
Hypotonia	0 (0.0)	2 (5.0)
Rash	1 (2.6)	2 (5.0)
Dermatitis diaper	0 (0.0)	2 (5.0)
Cataract operation (non-study eye)	3 (7.7)	6 (15.0)
Patients with at least one treatment-emergent AE related to treatment (Adverse drug reaction)	**3 (7.7)**	**2 (5.0)**
All adverse drug reactions reported in a treatment group		
Corneal oedema	1	0 (0.0)
Ocular hypertension	0 (0.0)	1 (2.5)
Intraocular pressure increased	2	1 (2.5)

Source: Table 2.-3 of the study report

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In conclusion, the two treatments had comparable and acceptable overall safety profiles.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In this section efficacy and safety results for subgroups formed based on gender, Race and Age will be summarized.

4.1 Gender Age and Race

For both treatment groups, there were more female subjects with Anterior Cell Grade of zero compared to their male counter parts (Table 23). The Durezol group had slightly higher percentages of subjects with Anterior Cell Grade of zero compared to Pred Forte, for both genders.

Table 23: Percentage of Subjects with Anterior Cell Grade of zero by Gender Subgroups at Day 15 (ITT)

Visit	Gender	Cell Count	Durezol (N=39) n (%)	Pred Forte (N=49) n (%)
Day 15	Male	Total	16	20
		0 cells	11 (68.7)	14 (70.0)
		>0 cells	5 (31.2)	6 (30.0)
	Female	Total	22	20
		0 cells	19 (86.4)	17 (85.0)
		>0 cells	3 (13.6)	3 (15.0)

Source: Reviewer's Analysis

For both treatment groups, subjects in the 0-27 Days age group had a 100% success rate of achieving Anterior Cell Grade of zero at Day 15. Subjects in the 2-3 years age group had the lowest percentage of subjects with Anterior Cell Grade of zero at Day 15 (Table 24).

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Table 24: Percentage of Subjects with Anterior Cell Grade of zero by Age Subgroups at Day 15 (ITT)

Visit	Age Group	Cell Count	Durezol (N=39) n (%)	Pred Forte (N=49) n (%)
Day 15	0-27 Days	Total	3	3
		0 cells	3 (100.0)	14 (70.0)
		>0 cells	0 (0.0)	0 (0.0)
	28 Days- 23 Months	Total	27	26
		0 cells	22 (81.5)	21 (80.8)
		>0 cells	5 (18.5)	5 (19.2)
	2- 3 Years	Total	8	11
		0 cells	5 (86.36)	7 (63.6)
		>0 cells	3 (37.5)	4 (36.4)

Source: Table 14.2.1.-2 of the study report

For both treatment groups, the percentage of subjects with anterior cell grade of zero at Day 15 was lower in Black or African American subjects compared to other races (Table 25).

Table 25: Percentage of Subjects with Anterior Cell Grade of by Race Subgroups at Day 15 (ITT)

Visit	Race	Cell Count	Durezol (N=39) n (%)	Pred Forte (N=49) n (%)
Day 15	White	Total	20	24
		0 cells	18 (90.0)	19 (79.2)
		>0 cells	2 (10.0)	5 (20.8)
	Black or African American	Total	9	9
		0 cells	3 (33.3)	5 (55.6)
		>0 cells	6 (66.7)	4 (44.4)
	Asian	Total	0	1
		0 cells	0 (0.0)	1 (100.0)
		>0 cells	0 (0.0)	0 (0.0)
	Multi-racial	Total	3	2
		0 cells	3 (100.0)	2 (100.0)
		>0 cells	0 (0.0)	0 (0.0)
	Other	Total	6	4
		0 cells	6 (100.0)	4 (100.0)
		>0 cells	0 (0.0)	0 (0.0)

Source: Table 14.2.1.-4 of the study report

For the key secondary endpoint, the proportions of subjects who had clear inflammation as measured by the Global Assessment of Inflammation score, the Durezol group had

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slightly higher proportion of subjects with a grade of zero at Day 15 for both male (56.2% vs. 50.0%) and female participants (56.5% vs. 50.0%; Table 26).

Table 26: Percentage of Subjects with Global Assessment Grade of zero by Gender Subgroups at Day 15 (ITT)

Visit	Gender	Cell Count	Durezol (N=39) n (%)	Pred Forte (N=49) n (%)
Day 15	Male	Total	16	20
		0 cells	9 (56.2)	10 (50.0)
		>0 cells	7 (43.7)	10 (50.0)
	Female	Total	23	20
		0 cells	13 (56.5)	10 (50.0)
		>0 cells	10 (43.5)	10 (50.0)

Source: Reviewer's Analysis

For both treatment groups, subjects in the 2-3 years age group had the lowest percentage of subjects with Global assessment score Grade of zero at Day 15. At Day 15, subjects in the 0-27 Days age group had a 100% success rate of Global assessment score Grade of zero in the Pred Forte group while the corresponding number is 66.7% in the Durezol group (Table 27). The summary of the Global assessment score by race is presented in Table 28.

Table 27: Percentage of Subjects with Global Assessment Grade of zero by Age Subgroups at Day 15 (ITT)

Visit	Age Group	Cell Count	Durezol (N=39) n (%)	Pred Forte (N=49) n (%)
Day 15	0-27 Days	Total	3	3
		0 cells	2 (66.7)	3 (100.0)
		>0 cells	1 (33.3)	0 (00.0)
	28 Days-23 Months	Total	28	26
		0 cells	17 (60.7)	12 (46.1)
		>0 cells	11 (39.3)	14 (53.8)
	2-3 Years	Total	8	11
		0 cells	3 (37.5)	5 (45.4)
		>0 cells	5 (62.5)	6 (54.5)

Source: Reviewer's Analysis

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Table 28: Percentage of Subjects with Global Assessment Grade of zero by Race Subgroups at Day 15 (ITT)

Visit	Race	Cell Count	Durezol (N=39) n (%)	Pred Forte (N=49) n (%)
Day 15	White	Total	21	24
		0 cells	12 (57.1)	11 (45.8)
		>0 cells	9 (42.9)	13 (54.2)
	Black African American	Total	9	9
		0 cells	2 (22.2)	2 (22.2)
		>0 cells	7 (77.8)	7 (77.8)
	Asian	Total	0	1
		0 cells	0 (0.0)	1 (100.0)
		>0 cells	0 (0.0)	0 (0.0)
	Multi-Racial	Total	3	2
		0 cells	3 (100.0)	2 (100.0)
		>0 cells	0 (0.0)	0 (0.0)
	Other	Total	6	4
		0 cells	5 (83.3)	4 (100.0)
		>0 cells	1 (16.7)	0 (0.0)

Source: Reviewer's Analysis

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed. Comparison of US versus non-US was not conducted as all sites were located within the US.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The efficacy and safety results from the Phase 3b study are considered as descriptive. There is no statistical issue identified in this review.

5.2 Collective Evidence

Based on the observed percentage of subjects with clear Anterior chamber cell, it appears that the two treatments have comparable performance. The results of the primary efficacy analyses were consistent in the subgroups formed based on age, gender and race. The two treatments had comparable safety profile. There were no deaths reported and there was no significant adverse event.

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5.3 Conclusions and Recommendations

The Phase 3b study didn't show marked difference in the success rates between the Durezol group and the Pred Forte group in clearing anterior chamber flare by Day 15. Both drugs appeared to have an acceptable safety profile with no deaths reported and no significant adverse events. The study results should however be interpreted with caution given that the sample size of this study was small, including 39 subjects in the Durezol group and 40 subjects in the Pred Forte group.

5.4 Labeling Recommendations

The changes made to the Adverse Reactions and Pediatric Use sections of the label are in agreement with the results of the safety data from this NDA. The Pediatric Use section of the label discusses comparability of the two treatments in terms of safety, and no efficacy data from this NDA was used in the revision. This reviewer has no edit on the proposed labeling.

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/s/

ABEL T ESHETE
02/26/2013

YAN WANG
02/26/2013
I concur.