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 #:	NDA 208742 S-013
Drug Name:	DEXTENZA (dexamethasone ophthalmic insert) 0.4 mg
Indication(s):	Treatment of ocular inflammation and pain following ophthalmic surgery and for the treatment of ocular itching associated with allergic conjunctivitis
Applicant:	Ocular Therapeutix, Inc.
Date(s):	Date submitted: June 28, 2024 PDUFA date: April 28, 2025
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Keywords:	NDA review, clinical studies

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1 EXECUTIVE SUMMARY

DEXTENZA, a 0.4 mg dexamethasone ophthalmic insert, has been approved for the treatment of ocular pain and inflammation following ophthalmic surgery, as well as the treatment of ocular itching associated with allergic conjunctivitis. To satisfy the requirements governed by the Pediatric Research Equity Act (PREA), Ocular Therapeutix, Inc. conducted a pediatric study (Study CLN-Protocol-0050) to evaluate the safety of DEXTENZA for the treatment of ocular pain and inflammation following cataract surgery. The study was a randomized, open-label, parallel-arm, active control, multicenter study in subjects aged 0 to 5 years.

The Applicant's primary efficacy variables included absence of pain (i.e., Face, Legs, Activity, Cry, Consolability (FLACC) score of '0') at 8 days post-surgery; absence of cells (i.e., score of '0') in anterior chamber of the study eye at 14 days post-surgery; absence of pain (i.e., FLACC score of '0') at 1, 14, 28, and 42 days post-surgery; anterior chamber cells score in the study eye at 1, 8, 14, and 28 days post-surgery plus 42 days post-surgery, and the need for rescue medication(s) and frequency of daily use.

The Applicant stated that the study was not designed to show statistical significance of DEXTENZA. There was no formal statistical testing, and all summaries were descriptive. There were no multiplicity adjustments made for the primary efficacy endpoints. Also, there was no formal sample size calculation performed for the study.

In the reviewed pediatric Study CLN-Protocol-0050, the study was open-label. There were no formal hypothesis and statistical testing proposed for the comparison of DEXTENZA to the active control, prednisolone acetate suspension 1% (PAS), only descriptive statistics were provided for the primary efficacy endpoints. For the efficacy of DEXTENZA in the adult subjects with ocular pain and inflammation following cataract surgery, all the three Phase 3 studies compared DEXTENZA with placebo (not PAS) in the double masked design. All studies had formal statistical hypothesis and testing. Moreover, PAS was approved in 1973, there were no clinical data found for either adult or pediatric studies. Therefore, the data is limited, and the evidence of efficacy was inconclusive for DEXTENZA comparable to PAS for the treatment of ocular inflammation and pain following cataract surgery in pediatric subjects.

2 INTRODUCTION

2.1 Overview

DEXTENZA is a dexamethasone insert that is inserted into the lacrimal canaliculus following ophthalmic surgery. It releases a 0.4 mg dose of dexamethasone for up to 30 days following insertion. DEXTENZA has been approved for the treatment of ocular pain following ophthalmic surgery since November 2018 (NDA 208742). The indication was expanded to include the inflammation following ophthalmic surgery in June 2019. In October 2021, DEXTENZA was also approved for the treatment of ocular itching associated with allergic conjunctivitis.

To satisfy the requirements governed by the Pediatric Research Equity Act (PREA), Ocular Therapeutix, Inc. conducted a pediatric study to assess the safety of DEXTENZA compared to an active control, prednisolone acetate suspension 1% (PAS), for the treatment of postoperative pain and inflammation following ocular cataract surgery for pediatric subjects. The study population originally included subjects aged 0 to 3 years. However, due to difficulty in enrollment, the clinical study protocol was amended to include subjects up through 5 years old.

The current submission contains the conducted pediatric study (Study CLN-Protocol-0050), and this review focuses on the pediatric study.

Table 1: Summary of Trial Reviewed

Trial ID	Design†	Treatment/Sample Size	Primary Efficacy Endpoint
CLN-Protocol-0050	R, PA, MC, AC, open-label	DEXTENZA: 37 PAS: 32	• Absence of pain (i.e., FLACC score of '0') at 8 days post-surgery • Absence of cells (i.e., score of '0') in anterior chamber of the study eye at 14 days post-surgery • Absence of pain (i.e., FLACC score of '0') at 1, 14, 28, and 42 days post-surgery • Anterior chamber cells score in the study eye at 1, 8, 14, and 28 days post-surgery plus 42 days post-surgery • Need for rescue medication(s) and frequency of daily use

Source: Reviewer's analyses.
† R: randomized; PA: parallel-arm; MC: multi-center; AC: active-controlled.

2.2 Data Sources

The clinical study report is located at the following location in the CDER electronic document room (EDR): \\CDSESUB1\evsprod\NDA208742\0287\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ocular-inflammation-pain\5351-stud-rep-contr\cln-protocol-0050.

The datasets and define files are located in EDR at: \\CDSESUB1\evsprod\NDA208742\0287\m5\datasets. Both SDTM and ADaM Datasets were submitted by the Applicant to the CDER EDR in SAS transport format. In the original submission, the Applicant did not submit the programs that were used to generate the results in the clinical study report. An Information Request (IR) was sent out on August 5, 2024, to seek the programs. The Applicant submitted the programs on August 23, 2024, and the programs are located in EDR at: \\CDSESUB1\evsprod\NDA208742\0296\m5\datasets\cln-protocol-0050\analysis.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The electronic datasets and define files submitted by the Applicant were of acceptable quality and were sufficient for validating study results.

3.2 Evaluation of Efficacy

Evaluation of efficacy was based on the pediatric study, which was a randomized, open-label, parallel-arm, active control, multicenter study in subjects aged 0 to 5 years.

3.2.1 Study CLN-Protocol-0050

3.2.1.1 Study Design and Endpoints

Study CLN-Protocol-0050 was a pediatric study. The primary objective was to assess the safety of DEXTENZA compared to an active control, PAS, for the treatment of postoperative pain and inflammation following ocular surgery for pediatric cataract. The study was conducted at 14 sites in the US from August 2020 until December 2023.

In the study, a total of approximately 60 subjects aged 0 to 5 years were planned to be treated with either DEXTENZA or PAS. It was expected that only one eye per subject would be treated. However, if a subject required bilateral surgery or subsequently required surgery in the contralateral eye during the study (even if the subject was >5 years of age at the time of the second surgery), the study treatment that was not assigned during randomization was used to treat the contralateral eye after the subject completed the last visit (Visit 7, 42 days post-surgery) for the first study eye. Following treatment of the second eye, the subject again completed the full visit schedule through the last visit (Visit 7, 42 days post-surgery).

Study duration was approximately 2 to 3 months from screening to the last visit (Visit 7, 42 Days post-surgery). There were 7 scheduled study visits. Visit 1 was the Screening Visit and occurred up to a maximum of 30 days prior to surgery/treatment. Visit 1 (Screening Visit) and Visit 2 (Day 1) could have been completed on the same day. Visit 2 (Day 1) was on the day of surgery. At the end of surgery on Visit 2, eligibility for enrollment into the study was assessed. Subjects who met eligibility criteria at both Visit 1 (Screening) and Visit 2 (Surgery/Treatment) were randomized in a 1:1 ratio to receive DEXTENZA or PAS.

For the eye randomized to receive DEXTENZA, the Investigator inserted DEXTENZA into the punctum of the study eye at the conclusion of the cataract surgery if the eye(s) did not experience any protocol-specific procedural exclusion criteria and punctum was successfully dilated. For the eye randomized to be treated with PAS, one drop was administered in the lower fornix at the end of surgery by the Investigator. Following that, subject's legally authorized representative (LAR) was instructed to administer 1 PAS drop in the lower fornix 4 times daily (QID) for a week, followed by 3 times daily (TID) for the next week, twice daily (BID) for the next week, and once a day for the last week. Due to the different dosing regimen between DEXTENZA and PAS, the Investigators and subjects were not masked to the treatment assignment in the study.

Treated subjects completed post-surgery study Visits 3 through 7 (1, 8, 14, 28, and 42 days post-surgery, respectively).

The primary efficacy endpoints were:

- Absence of pain (i.e., FLACC score of '0') at 8 days post-surgery
- Absence of cells (i.e., score of '0') in anterior chamber of the study eye at 14 days post-surgery
- Absence of pain (i.e., FLACC score of '0') at 1, 14, 28, and 42 days post-surgery
- Anterior chamber cells score in the study eye at 1, 8, 14, and 28 days post-surgery plus 42 days post-surgery
- Need for rescue medication(s) and frequency of daily use

Exploratory evaluations included:

- Presence of DEXTENZA after insertion and at all visits through the Day 28 visit
- Ease of DEXTENZA use (insertion) as assessed by the Investigator at Visit 2 (Surgery/Treatment)
- Ease of DEXTENZA visualization at all visits through the Day 28 visit as assessed by the Investigator

3.2.1.2 Statistical Methodologies

Primary Efficacy Analysis

The primary analysis was performed on safety population which included all subjects who received an investigational study medication (DEXTENZA or PAS). All analyses performed on the safety population will be according to the treatment the subjects received. One subject can have both eyes as study eyes.

The study was not designed to show statistical significance of DEXTENZA, and there was no formal statistical testing. All summaries were descriptive.

Sensitivity Analysis

Subjects were allowed to use rescue medications. Furthermore, there were missing data in the study. The Applicant did not conduct any sensitivity analyses to evaluate the impact of the rescue medication use and missing data on the descriptive analyses. For ocular pain scores, the reviewer performed a sensitivity analysis where subjects using rescue medications were treated as having ocular pain post-surgery. The reviewer also performed a conservative sensitivity analysis where subjects with missing ocular pain score at 8 days post-surgery in the DEXTENZA group were treated as having ocular pain at 8 days post-surgery and subjects with missing ocular pain score at 8 days post-surgery in the PAS group were treated as not having ocular pain at 8 days post-surgery.

Type I Error Control

As there were no formal hypothesis tests, no multiplicity adjustments were made in the study.

Sample Size Calculation

The Applicant stated that there was no formal sample size calculation performed for the study. The study included approximately 60 subjects from 14 investigator sites. It was stated in the statistical analysis plan (SAP) that "The sample size will allow for safety information to be obtained and have 95% probability of detecting an adverse event that occurs at a true rate of 10% or greater. Statistical analyses will be descriptive."

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

The disposition of all randomized subjects is shown in Table 2. Of the 68 subjects screened, 67 were randomized. Two subjects were randomized but not treated because the subject was unable to have surgery within 30 days of screening (Subject (b) (6)) or too much time elapsed between screening and surgery (Subject (b) (6)). One subject (Subject (b) (6)) was a randomization failure but was randomized and treated with PAS. Subject (b) (6) was randomized to PAS but inadvertently treated with DEXTENZA. Four subjects received the study treatment for the second eye. Of the 69 total treated eyes, all remained on study treatment until the study completion at 42 days post-surgery. There was no discontinuation of study treatment.

The demographic and baseline ocular characteristics in the study eyes for all subjects in the safety population are presented in the appendix (Table 14 and Table 15). Overall, 62.3% of the subjects were male and 88.4% were not Hispanic or Latino, and the mean age was 1.3 years (range: 0 - 4 years). The anterior chamber cells and anterior chamber flare grading for the study eye were similar between treatment groups (Table 15). Intraocular pressure (IOP) for the study eye was also comparable between treatment groups. The anterior chamber cells and anterior chamber flare grading for the non-study eye were similar between treatment groups (Table 15). IOP for the non-study eye was also comparable between treatment groups. FLACC pain scores were similar between treatment groups, with mean (SD) of 0.2 (1.32) for the DEXTENZA group and 0.4 (1.88) for the PAS control group (Table 15).

Table 2: Subject Disposition

Characteristic, n (%)	DEXTENZA	PAS	Overall
Screened			68
Screened Not Randomized [1]			1
Randomized [2]	34	33	67
Randomized Not Treated [2]	1	1	2
Treated Eyes – Total	37	32	69
Treated Eyes – Initial Treatment	34	31	65
Treated as Randomized	33	31	64
Treated not as Randomized [4]	1	0	1
Treated – The Second Eye Treatment	3	1	4
Safety Analysis Population [3]	37 (100)	32 (100)	69
Study Completion			
Completed	37 (100)	32 (100)	69
Discontinued	0	0	0

Source: Reviewer's analyses; Clinical Study Report Table 14.1.1.
Abbreviations: PAS=prednisolone acetate suspension.
[1] Subject (b) (6) was not randomized.
[2] Subjects (b) (6) and (b) (6) were randomized but not treated. Subject (b) (6) who was a randomization failure due to not meeting all inclusion and exclusion criteria but randomized and treated. This subject was included in the Safety population.

[3] Percentages were based on the total number of treated eyes consisting of the treated eyes that received the initial treatment and the treated second eyes from 4 subjects who had completed the initial study eye treatment.
[4] Subject (b) (6) was randomized to PAS but inadvertently treated with DEXTENZA.

3.2.1.4 Results and Conclusions

There was a total of 69 study eyes included in the safety population. Thirty-seven study eyes were treated with DEXTENZA and 32 study eyes were treated with PAS. Four subjects had the second eye treatments (Table 3).

Table 3: Subjects Had the Second Eye Treatments

Subject	Age	First Eye Treatment	Second Eye Treatment
(b) (6)	0	PAS	DEXTENZA
	3	DEXTENZA	PAS
	3	PAS	DEXTENZA
*	4	PAS	DEXTENZA

Source: Reviewer's analyses
*: The second eye was treated when the subject past age 5 for 17 days.

Primary Efficacy Results

As previously described in the section of Statistical Methodologies, there was no formal statistical testing and therefore, the study was not powered to achieve statistical significance. All summaries were descriptive.

Absence of Pain at 8 Days Post-Surgery

At 8 days post-surgery, a total of 35/36 (97.2%) study eyes did not have ocular pain (FLACC score of '0') in the DEXTENZA group, while 27/29 (93.1%) study eyes in the PAS group did not have ocular pain (Table 4).

Table 4: Absence of Ocular Pain at 8 Days Post-Surgery

Absence of Ocular Pain at 8 Days Post-Surgery	DEXTENZA (N=37)	PAS (N=32)	Overall (N=69)
n [1] [2]	36	29	65
Yes	35 (97.2%)	27 (93.1%)	62 (95.4%)
No	1 (2.8%)	2 (6.9%)	3 (4.6%)

Source: Reviewer's analysis
[1] n is the number of treated eyes from those subjects (including subjects who received the second eye treatment) who had observed FLACC pain data.
[2] Data observed after subjects received rescue medications were included in the efficacy summary.

At 8 days post-surgery, 3 (8.1%) treated eyes in the DEXTENZA group and 3 (9.4%) treated eyes in the PAS group used rescue medications. Efficacy data observed after subjects received rescue medications were included in the summary of Table 4. To evaluate the impact of the use of rescue medications on the absence of pain at 8 days post-surgery, the reviewer conducted a sensitivity analysis where eyes using rescue medications were treated as having ocular pain at 8 days post-surgery (Table 5). As the DEXTENZA and PAS group had similar proportions of subjects using rescue medications, the comparison of the two treatment groups in the sensitivity analysis is similar to that in Table 4.

Table 5: Absence of Ocular Pain at 8 Days Post-Surgery

Absence of Ocular Pain at 8 Days Post-Surgery [2]	DEXTENZA (N=37)	PAS (N=32)	Overall (N=69)
n [1]	36	29	65
Yes	32 (88.9%)	24 (82.8%)	56 (86.2%)
No	4 (11.1%)	5 (17.2%)	9 (13.8%)

Source: Reviewer's analysis
[1] n is the number of treated eyes from those subjects (including subjects who received the second eye treatment) who had observed FLACC pain data.
[2] Subjects using rescue medications were treated as having ocular pain at 8 days post-surgery.

Furthermore, 1 (2.7%) treated eyes in the DEXTENZA group and 3 (9.4%) treated eyes in the PAS group had missing ocular pain scores at 8 days post-surgery. To evaluate whether the descriptive statistics are robust to the handling of missing data, the reviewer conducted a conservative sensitivity analysis where subjects with missing ocular pain score at 8 days post-surgery in the DEXTENZA group were treated as having ocular pain at 8 days post-surgery and subjects with missing ocular pain score at 8 days post-surgery in the PAS group were treated as not having ocular pain at 8 days post-surgery (Table 6).

Table 6: Absence of Ocular Pain at 8 Days Post-Surgery

Absence of Ocular Pain at 8 Days Post-Surgery	DEXTENZA (N=37)	PAS (N=32)	Overall (N=69)
n [1] [2][3]	37	32	69
Yes	35 (94.6%)	30 (93.4%)	65 (94.2%)
No	2 (5.4%)	2 (6.6%)	4 (5.8%)

Source: Reviewer's analysis
[1] n is the number of treated eyes from those subjects (including subjects who received the second eye treatment) who had observed FLACC pain data.
[2] Data observed after subjects received rescue medications were included in the efficacy summary.
[3] Subjects with missing ocular pain score at 8 days post-surgery in the DEXTENZA group were treated as having ocular pain at 8 days post-surgery; subjects with missing ocular pain score at 8 days post-surgery in the PAS group were treated as not having ocular pain at 8 days post-surgery.

Absence of Anterior Chamber Cells at 14 Days Post-Surgery

The proportion of study eyes with the absence of anterior chamber cells at 14 days post-surgery was 80.6% (25/31) in the DEXTENZA group and 73.1% (19/26) in the PAS control group (Table 7). It should be noted that there was a high rate of missing data for anterior chamber cells as they were counted via slit lamp examination and were difficult to obtain due to the nature of the young pediatric population (mean age was 1 year old, with 43/65 (66.2%) subjects aged 1 year or younger).

Table 7: Absence of Anterior Chamber Cells at 14 Days Post-Surgery

Absence of Anterior Chamber Cells at 14 Days Post-Surgery	DEXTENZA (N=37)	PAS (N=32)	Overall (N=69)
n [1]	31	26	57
Yes	25 (80.6%)	19 (73.1%)	44 (77.2%)
No	6 (19.4%)	7 (26.9%)	13 (22.8%)

Source: Reviewer's analysis
[1] n is the number of treated eyes from those subjects (including subjects who received the second eye treatment) who had observed anterior chamber cells.

Ocular Pain FLACC Scores at 1, 8, 14, 28 and 42 Days Post-Surgery

Summary of ocular pain FLACC scores and mean change from baseline by visit is presented in Table 8.

At Visit 3 (1 day post-surgery), FLACC ocular pain scores had a mean (SD) of 0.4 (1.14) for the DEXTENZA group and 0.7 (1.49) for the PAS control group. A total of 32/37 (86.5%) and 26/32 (81.3%) study eyes had a FLACC score of 0 at 1 day post-surgery in the DEXTENZA group and PAS control group, respectively.

At Visit 4 (8 days post-surgery), FLACC ocular pain scores had a mean (SD) of 0.1 (0.33) for the DEXTENZA group and 0.2 (0.82) for the PAS control group. A total of 35/36 (97.2%) and 27/29 (93.1%) study eyes had a FLACC score of 0 at 8 days post-surgery in the DEXTENZA group and PAS control group, respectively.

At Visit 5 (14 days post-surgery), FLACC ocular pain scores had a mean (SD) of 0.1 (0.36) for the DEXTENZA group and 0.2 (0.88) for the PAS control group. A total of 35/37 (94.6%) and 31/32 (96.9%) study eyes had a FLACC score of 0 at 14 days post-surgery in the DEXTENZA group and PAS control group, respectively.

At Visit 6 (28 days post-surgery), FLACC ocular pain scores had a mean (SD) of 0.2 (0.88) for the DEXTENZA group and 0.2 (0.79) for the PAS control group. A total of 35/37 (94.6%) and 29/31 (93.5%) study eyes had a FLACC score of 0 at 28 days post-surgery in the DEXTENZA group and PAS control group, respectively.

At Visit 7 (42 days post-surgery), FLACC ocular pain scores had a mean (SD) of 0.1 (0.66) for the DEXTENZA group and 0.0 (0.00) for the PAS control group. A total of 36/37 (97.3%) and 32/32 (100%) study eyes had a FLACC score of 0 at 42 days post-surgery in the DEXTENZA group and PAS control group, respectively.

The mean change from baseline of ocular pain FLACC scores is also presented in Figure 1.

For the four subjects with bilateral eye treatments, their FLACC scores for the two treated eyes were presented in Table 9.

At 8 days post-surgery, 3 (8.1%) treated eyes in the DEXTENZA group and 3 (9.4%) treated eyes in the PAS group used rescue medications. At 14 days post-surgery, 5 (13.5%) treated eyes in the DEXTENZA group and 4 (12.5%) treated eyes in the PAS group used rescue medications. At 28 days post-surgery, 5 (13.5%) treated eyes in the DEXTENZA group and 4 (12.5%) treated eyes in the PAS group used rescue medications. At 42 days post-surgery, 6 (16.2%) treated eyes in the DEXTENZA group and 4 (12.5%) treated eyes in the PAS group used rescue medications. Efficacy data observed after subjects received rescue medications were included in the summary of Table 8. As the DEXTENZA and PAS group had similar proportions of subjects using rescue medications, the use of rescue medications would not have a big impact on the comparison of the two treatment groups for ocular pain FLACC scores at 8, 14, 28 and 42 days post-surgery.

Furthermore, at 8 days post-surgery, 1 (2.7%) treated eyes in the DEXTENZA group and 3 (9.4%) treated eyes in the PAS group had missing ocular pain scores at 8 days post-surgery. A conservative sensitivity analysis has been conducted to evaluate the impact of the missing data on the descriptive statistics for ocular pain scores at 8 days post-surgery (Table 6). As there were no missing ocular pain scores at 14 days and 42 days post-surgery, and there was only 1 missing ocular pain score at 28 days post-surgery, the impact of the missing data on the ocular pain scores at 14, 28, and 42 days post-surgery can be neglected.

Anterior Chamber Cells Score at 1, 8, 14, 28 and 42 Days Post-Surgery

The anterior chamber cells score in the study eye was collected at post-surgery 1, 8, 14, 28, and 42 days. At Screening, all graded study eyes in DEXTENZA group (33 study eyes) and PAS control group (31 study eyes) had an anterior chamber cells score of 0 (Table 10).

At Visit 3 (1 day post-surgery), the proportion of study eyes with an anterior chamber cells score of 0 was 18/28 (64.3%) in the DEXTENZA group and 13/26 (50.0%) in the PAS control group.

At Visit 4 (8 days post-surgery), the proportion of study eyes with an anterior chamber cells score of 0 was 18/29 (62.1%) in the DEXTENZA group and 17/26 (65.4%) in the PAS control group.

At Visit 5 (14 days post-surgery), the proportion of study eyes with an anterior chamber cells score of 0 was 25/31 (80.6%) in the DEXTENZA group and 19/26 (73.1%) in the PAS control group.

At Visit 6 (28 days post-surgery), the proportion of study eyes with an anterior chamber cells score of 0 was 30/30 (100%) in the DEXTENZA group and 25/27 (92.6%) in the PAS control group.

At Visit 7 (42 days post-surgery), the proportion of study eyes with an anterior chamber cells score of 0 was 30/32 (93.8%) in the DEXTENZA group and 26/27 (96.3%) in the PAS control group.

It should be noted that there was a high rate of missing data for anterior chamber cells as they were counted via slit lamp examination and were difficult to obtain due to the nature of the young pediatric population (mean age was 1 year old, with 43/65 (66.2%) subjects aged 1 year or younger).

For the four subjects with bilateral eye treatments, their anterior chamber cells scores for the two treated eyes were displayed in Table 11.

Use of Rescue Medications

Rescue use at each visit is shown in Table 12. Most study eyes did not use rescue medications throughout the study. By Visit 7 (42 days post-surgery), 6/37 (16.2%) study eyes in the DEXTENZA group and 4/32 (12.5%) study eyes in the PAS control group received rescue medications (Table 12).

For the four subjects with bilateral eye treatments, their rescue medication uses for the two treated eyes were displayed in Table 13.

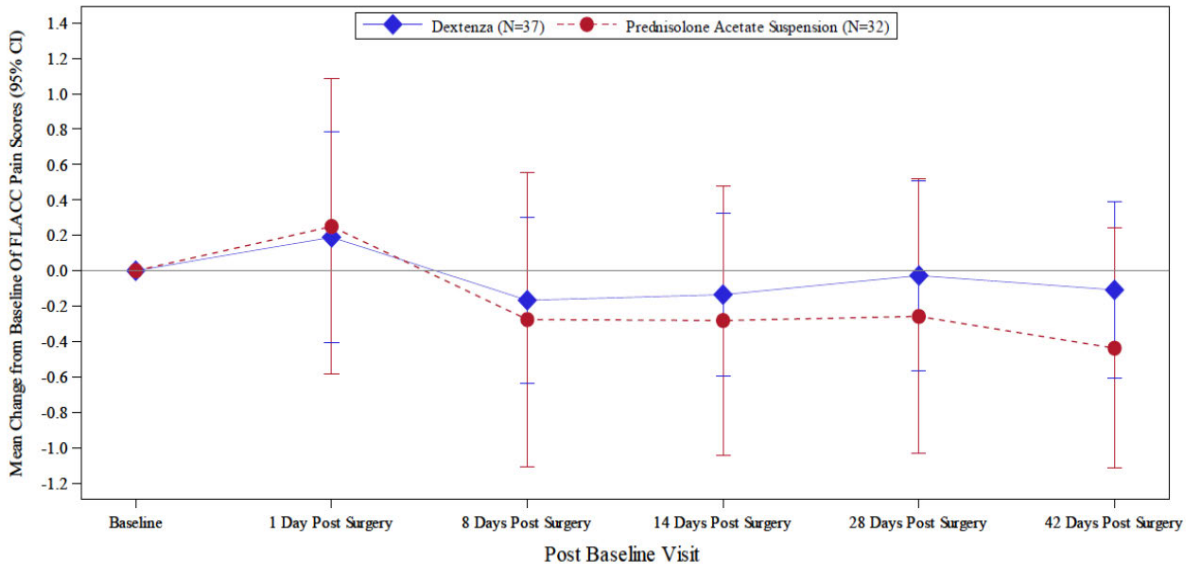
Table 8: Summary of Ocular Pain FLACC Scores and Mean Change from Baseline by Visit (Safety Population)

Parameter Category, n (%)	Dextenza (N=37)	PAS (N=32)	Overall (N=69)
Baseline			
n [1]	37	32	69
0	36 (97.3)	30 (93.8)	66 (95.7)
1 to 2	0	0	0
3 to 4	0	1 (3.1)	1 (1.4)
5 to 6	0	0	0
7 to 8	1 (2.7)	0	1 (1.4)
9 to 10	0	1 (3.1)	1 (1.4)
n	37	32	69
Mean (SD)	0.2 (1.32)	0.4 (1.88)	0.3 (1.59)
Median	0.0	0.0	0.0
Min, Max	0, 8	0, 10	0, 10
Visit 3 (1 Day Post-Surgery)			
n [1]	37	32	69
0	32 (86.5)	26 (81.3)	58 (84.1)
1 to 2	1 (2.7)	0	1 (1.4)
3 to 4	3 (8.1)	5 (15.6)	8 (11.6)
5 to 6	1 (2.7)	1 (3.1)	2 (2.9)
7 to 8	0	0	0
9 to 10	0	0	0
n	37	32	69
Mean (SD)	0.4 (1.14)	0.7 (1.49)	0.5 (1.31)
Median	0.0	0.0	0.0
Min, Max	0, 5	0, 5	0, 5
Change from Baseline to Visit 3 (1 Day Post-Surgery)			
n	37	32	69
Mean (SD)	0.2 (1.79)	0.3 (2.31)	0.2 (2.04)
Median	0.0	0.0	0.0
Min, Max	-8, 5	-10, 5	-10, 5
Visit 4 (8 Days Post-Surgery)			
n [1]	36	29	65
0	35 (97.2)	27 (93.1)	62 (95.4)
1 to 2	1 (2.8)	1 (3.4)	2 (3.1)
3 to 4	0	1 (3.4)	1 (1.5)
5 to 6	0	0	0
7 to 8	0	0	0
9 to 10	0	0	0
n	36	29	65
Mean (SD)	0.1 (0.33)	0.2 (0.82)	0.1 (0.60)
Median	0.0	0.0	0.0
Min, Max	0, 2	0, 4	0, 4
Change from Baseline to Visit 4 (8 Days Post-Surgery)			
n	36	29	65
Mean (SD)	-0.2 (1.38)	-0.3 (2.19)	-0.2 (1.77)
Median	0.0	0.0	0.0
Min, Max	-8, 2	-10, 4	-10, 4
Visit 5 (14 Days Post-Surgery)			
n [1]	37	32	69
0	35 (94.6)	31 (96.9)	66 (95.7)

Parameter Category, n (%)	Dextenza (N=37)	PAS (N=32)	Overall (N=69)
1 to 2	2 (5.4)	0	2 (2.9)
3 to 4	0	0	0
5 to 6	0	1 (3.1)	1 (1.4)
7 to 8	0	0	0
9 to 10	0	0	0
n	37	32	69
Mean (SD)	0.1 (0.36)	0.2 (0.88)	0.1 (0.65)
Median	0.0	0.0	0.0
Min, Max	0, 2	0, 5	0, 5
Change from Baseline to Visit 5 (14 Days Post-Surgery)			
n	37	32	69
Mean (SD)	-0.1 (1.38)	-0.3 (2.11)	-0.2 (1.75)
Median	0.0	0.0	0.0
Min, Max	-8, 2	-10, 5	-10, 5
Visit 6 (28 Days Post-Surgery)			
n [1]	37	31	68
0	35 (94.6)	29 (93.5)	64 (94.1)
1 to 2	1 (2.7)	1 (3.2)	2 (2.9)
3 to 4	0	1 (3.2)	1 (1.5)
5 to 6	1 (2.7)	0	1 (1.5)
7 to 8	0	0	0
9 to 10	0	0	0
n	37	31	68
Mean (SD)	0.2 (0.88)	0.2 (0.79)	0.2 (0.83)
Median	0.0	0.0	0.0
Min, Max	0, 5	0, 4	0, 5
Change from Baseline to Visit 6 (28 Days Post-Surgery)			
n	37	31	68
Mean (SD)	0.0 (1.61)	-0.3 (2.11)	-0.1 (1.84)
Median	0.0	0.0	0.0
Min, Max	-8, 5	-10, 4	-10, 5
Visit 7 (42 Days Post-Surgery)			
n [1]	37	32	69
0	36 (97.3)	32 (100)	68 (98.6)
1 to 2	0	0	0
3 to 4	1 (2.7)	0	1 (1.4)
5 to 6	0	0	0
7 to 8	0	0	0
9 to 10	0	0	0
n	37	32	69
Mean (SD)	0.1 (0.66)	0.0 (0.00)	0.1 (0.48)
Median	0.0	0.0	0.0
Min, Max	0, 4	0, 0	0, 4
Change from Baseline to Visit 7 (42 Days Post-Surgery)			
n	37	32	69
Mean (SD)	-0.1 (1.49)	-0.4 (1.88)	-0.3 (1.68)
Median	0.0	0.0	0.0
Min, Max	-8, 4	-10, 0	-10, 4

Source: Reviewer's analysis and Clinical Study Report Table 14.2.2.3.
Data observed after subjects received rescue medications were included in the efficacy summary.

Figure 1: Mean Change from Baseline of Ocular Pain FLACC Scores (Safety population)



Source: Clinical Study Report Figure 14.2.2.3.1.
Data observed after subjects received rescue medications were included.

Table 9: FLACC Scores for Subjects with Bilateral Eye Treatments

Subject (b) (6)	Study Eye using PAS	Second Study Eye using DEXTENZA
Baseline	0	0
1 Day Post-Surgery	0	0
8 Days Post-Surgery	0	0
14 Days Post-Surgery	0	0
28 Days Post-Surgery	0	0
42 Days Post-Surgery	0	0

Subject (b) (6)	Study Eye using DEXTENZA	Second Study Eye using PAS
Baseline	0	0
1 Day Post-Surgery	0	3
8 Days Post-Surgery	0	0
14 Days Post-Surgery	0	0
28 Days Post-Surgery	0	0
42 Days Post-Surgery	0	0

Subject (b) (6)	Study Eye using PAS	Second Study Eye using DEXTENZA
Baseline	0	0
1 Day Post-Surgery	0	0
8 Days Post-Surgery	0	0
14 Days Post-Surgery	0	0
28 Days Post-Surgery	0	0
42 Days Post-Surgery	0	0

Subject (b) (6)	Study Eye using PAS	Second Study Eye using DEXTENZA
Baseline	0	8
1 Day Post-Surgery	0	0
8 Days Post-Surgery	0	0
14 Days Post-Surgery	0	0
28 Days Post-Surgery	0	0
42 Days Post-Surgery	0	0

Source: Reviewer's analysis.

Table 10: Anterior Chamber Cells in the Study Eye by Visit (Safety Population)

Visit Category, n (%)	Dextenza (N=37)	PAS (N=32)	Overall (N=69)
Visit 1 (Screening)			
n [1]	33	31	64
Grade 0	33 (100)	31 (100)	64 (100)
Grade 0.5	0	0	0
Grade 1+	0	0	0
Grade 2+	0	0	0
Grade 3+	0	0	0
Grade 4+	0	0	0
Visit 3 (1 Day Post-Surgery)			
n [1]	28	26	54
Grade 0	18 (64.3)	13 (50.0)	31 (57.4)
Grade 0.5	0	4 (15.4)	4 (7.4)
Grade 1+	8 (28.6)	8 (30.8)	16 (29.6)
Grade 2+	2 (7.1)	1 (3.8)	3 (5.6)
Grade 3+	0	0	0
Grade 4+	0	0	0
Visit 4 (8 Days Post-Surgery)			
n [1]	29	26	55
Grade 0	18 (62.1)	17 (65.4)	35 (63.6)
Grade 0.5	7 (24.1)	6 (23.1)	13 (23.6)
Grade 1+	2 (6.9)	3 (11.5)	5 (9.1)
Grade 2+	1 (3.4)	0	1 (1.8)
Grade 3+	0	0	0
Grade 4+	1 (3.4)	0	1 (1.8)
Visit 5 (14 Days Post-Surgery)			
n [1]	31	26	57
Grade 0	25 (80.6)	19 (73.1)	44 (77.2)
Grade 0.5	5 (16.1)	5 (19.2)	10 (17.5)
Grade 1+	1 (3.2)	1 (3.8)	2 (3.5)
Grade 2+	0	0	0
Grade 3+	0	0	0
Grade 4+	0	1 (3.8)	1 (1.8)
Visit 6 (28 Days Post-Surgery)			
n [1]	30	27	57
Grade 0	30 (100)	25 (92.6)	55 (96.5)
Grade 0.5	0	1 (3.7)	1 (1.8)
Grade 1+	0	1 (3.7)	1 (1.8)
Grade 2+	0	0	0
Grade 3+	0	0	0
Grade 4+	0	0	0
Visit 7 (42 Days Post-Surgery)			
n [1]	32	27	59
Grade 0	30 (93.8)	26 (96.3)	56 (94.9)
Grade 0.5	1 (3.1)	1 (3.7)	2 (3.4)
Grade 1+	1 (3.1)	0	1 (1.7)
Grade 2+	0	0	0
Grade 3+	0	0	0
Grade 4+	0	0	0

Source: Reviewer's analysis and Clinical Study Report Table 14.2.2.2.

Table 11: Anterior Chamber Cells Scores for Subjects with Bilateral Eye Treatments

Subject (b) (6)	Study Eye using PAS	Second Study Eye using DEXTENZA
Baseline	Grade 0	Grade 0
1 Day Post-Surgery	Grade 1+	Grade 1+
8 Days Post-Surgery	Grade 0.5	Grade 0.5
14 Days Post-Surgery	Grade 0.5	Grade 0
28 Days Post-Surgery	Grade 0	Grade 0
42 Days Post-Surgery	Grade 0	Grade 0

Subject (b) (6)	Study Eye using DEXTENZA	Second Study Eye using PAS
Baseline	Grade 0	Grade 0
1 Day Post-Surgery	Grade 2+	Grade 2+
8 Days Post-Surgery	Grade 1+	Grade 0.5
14 Days Post-Surgery	Grade 0.5	Grade 0.5
28 Days Post-Surgery	Grade 0	Grade 0
42 Days Post-Surgery	Grade 0	Grade 0

Subject (b) (6)	Study Eye using PAS	Second Study Eye using DEXTENZA
Baseline	Grade 0	Grade 0
1 Day Post-Surgery	Grade 0	Grade 0
8 Days Post-Surgery	Grade 0	Grade 0
14 Days Post-Surgery	Grade 0	Grade 0
28 Days Post-Surgery	Grade 0	Grade 0
42 Days Post-Surgery	Grade 0	Grade 0

Subject (b) (6)	Study Eye using PAS	Second Study Eye using DEXTENZA
Baseline	Grade 0	Grade 0
1 Day Post-Surgery	Grade 1+	Grade 1+
8 Days Post-Surgery	Grade 0.5	Grade 0.5
14 Days Post-Surgery	Grade 0.5	Grade 0.5
28 Days Post-Surgery	Grade 0	Grade 0
42 Days Post-Surgery	Grade 0	Grade 0

Source: Reviewer's analysis.

Table 12: Rescue Medication Use in the Study Eye by Duration (Safety Population)

Duration Parameter Category, n (%)/Statistic	DEXTENZA (N=37)	PAS (N=32)	Overall (N=69)
Rescue Medications on or Prior to Visits			
Visit 1 (Screening)			
N [1]	37	32	69
Used Rescue Medications	0	0	0
Not Used Rescue Medications	37 (100)	32 (100)	69 (100)
Visit 3 (1 Day Post-Surgery)			
N [1]	37	32	69
Used Rescue Medications	0	0	0
Not Used Rescue Medications	37 (100)	32 (100)	69 (100)
Visit 4 (8 Days Post-Surgery)			
N [1]	37	32	69
Used Rescue Medications	3 (8.1)	3 (9.4)	6 (8.7)
Not Used Rescue Medications	34 (91.9)	29 (90.6)	63 (91.3)
Visit 5 (14 Days Post-Surgery)			
N [1]	37	32	69
Used Rescue Medications	5 (13.5)	4 (12.5)	9 (13.0)
Not Used Rescue Medications	32 (86.5)	28 (87.5)	60 (87.0)
Visit 6 (28 Days Post-Surgery)			
N [1]	37	32	69
Used Rescue Medications	5 (13.5)	4 (12.5)	9 (13.0)
Not Used Rescue Medications	32 (86.5)	28 (87.5)	60 (87.0)
Visit 7 (42 Days Post-Surgery)			
N [1]	37	32	69
Used Rescue Medications	6 (16.2)	4 (12.5)	10 (14.5)
Not Used Rescue Medications	31 (83.8)	28 (87.5)	59 (85.5)

Source: Reviewer's analysis.

Table 13: Rescue Medication Use for Subjects with Bilateral Eye Treatments

Subject (b) (6)	Study Eye using PAS	Second Study Eye using DEXTENZA
Baseline	No	No
1 Day Post-Surgery	No	No
8 Days Post-Surgery	No	No
14 Days Post-Surgery	No	No
28 Days Post-Surgery	No	No
42 Days Post-Surgery	No	No

Subject (b) (6)	Study Eye using DEXTENZA	Second Study Eye using PAS
Baseline	No	No
1 Day Post-Surgery	No	No
8 Days Post-Surgery	No	No
14 Days Post-Surgery	No	No
28 Days Post-Surgery	No	No
42 Days Post-Surgery	No	No

Subject (b) (6)	Study Eye using PAS	Second Study Eye using DEXTENZA
Baseline	No	No
1 Day Post-Surgery	No	No
8 Days Post-Surgery	Yes	No
14 Days Post-Surgery	Yes	Yes
28 Days Post-Surgery	Yes	Yes
42 Days Post-Surgery	Yes	Yes

Subject (b) (6)	Study Eye using PAS	Second Study Eye using DEXTENZA
Baseline	No	No
1 Day Post-Surgery	No	No
8 Days Post-Surgery	No	No
14 Days Post-Surgery	No	No
28 Days Post-Surgery	No	No
42 Days Post-Surgery	No	No

Source: Reviewer's analysis.

Conclusion of Efficacy

In the reviewed pediatric Study CLN-Protocol-0050, the study was open-label. There was no formal hypothesis and statistical testing proposed for the comparison of DEXTENZA to the active control, prednisolone acetate suspension 1% (PAS), only descriptive statistics were provided for the primary efficacy endpoints. For the efficacy of DEXTENZA in the adult subjects with ocular pain and inflammation following cataract surgery, all the three Phase 3 studies compared DEXTENZA with placebo (not PAS) in the double masked design. All studies had formal statistical hypothesis and testing. Moreover, PAS was approved in 1973, there were no clinical data found for either adult or pediatric studies. Therefore, the data is limited, and the evidence of efficacy was inconclusive for DEXTENZA comparable to PAS for the treatment of ocular inflammation and pain following cataract surgery in pediatric subjects.

3.3 Evaluation of Safety

The Applicant stated that DEXTENZA was demonstrated to be safe in the pediatric population with safety observations similar to the PAS control group. There were no deaths or study discontinuations. There was one ocular serious adverse event (SAE) of iritis reported in the PAS control group and no non-ocular SAEs reported in either treatment group. The SAE of iritis was severe and considered unrelated to the investigational product (IP) but related to the study procedure (cataract surgery). The dose of PAS was subsequently increased, and the event resolved 34 days later.

A total of 18/37 (48.6%) study eyes reported at least one ocular treatment-emergent adverse event (TEAE) in the DEXTENZA group compared with 10/32 (31.3%) in the PAS control group. Most ocular TEAEs were considered mild or moderate in severity and considered unrelated to the IP. The most common ocular TEAEs reported greater than 5% in any treatment group were IOP increased (7/37 [18.9%] in the DEXTENZA group and 3/32 [9.4%] in the PAS control group), anterior capsule contraction (2/37 [5.4%] in the DEXTENZA group and 1/32 [3.1%] in the PAS control group), and conjunctival hyperemia (0 in the DEXTENZA group and 2/32 [6.3%] in the PAS control group).

The Applicant stated that IOP increase was also observed in four studies conducted in adults that compared DEXTENZA to placebo vehicle for the treatment of ocular inflammation and pain after cataract surgery. The observed rates of increased IOP in the pediatric population were expected, since pediatric cataract surgery is a more complex surgery with greater risks of complications compared to adult cataract surgery. Pediatric cataract surgery is conducted in individuals with congenital cataracts who often have other underlying conditions. All of these IOP events (except for one) in the pediatric study were resolved. One subject ((b) (6)), who had one study eye treated with DEXTENZA and the other eye treated with PAS, presented with IOP elevations in both eyes on Day 9 post surgery. The subject was treated with ophthalmic dorzolamide hydrochloride/timolol maleate BID until study exit. The event of intermittent IOP increased reported in both eyes was assessed as moderate and related to cataract surgery. IOP was 15 mmHg in both eyes at study exit (42 days post-surgery).

In addition, the Applicant stated that there were no safety concerns identified from the results in the visual acuity, slit lamp biomicroscopy, IOP, and dilated fundus examinations. The reader is referred to Dr. Wadhwa's review for detailed information regarding the adverse event profile.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

As there was no formal statistical testing, the study was not powered to achieve statistical significance. All summaries were descriptive. Neither the Applicant nor the reviewer conducted subgroup analyses.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Study CLN-Protocol-0050 was a randomized, open-label, parallel-arm, active control, multicenter study designed to evaluate the safety of DEXTENZA for the treatment of ocular inflammation and pain after surgery for pediatric cataract. The study was not powered to achieve statistical significance. There was no formal statistical testing, and all summaries were descriptive. There were no multiplicity adjustments made for primary efficacy endpoints in the study. Also, there were no formal sample size calculation performed for the study.

5.2 Collective Evidence

For the Phase 3 Study CLN-Protocol-0050, the efficacy of DEXTENZA was evaluated by the primary endpoints: absence of pain at 8 days post-surgery; absence of cells in anterior chamber of the study eye at 14 days post-surgery; absence of pain at 1, 14, 28, and 42 days post-surgery; anterior chamber cells score in the study eye at 1, 8, 14, and 28 days post-surgery plus 42 days post-surgery, and need for rescue medication(s) and frequency of daily use.

In the reviewed pediatric Study CLN-Protocol-0050, only descriptive statistics were provided for the primary efficacy endpoints. There were no formal hypothesis and statistical testing proposed for the comparison of DEXTENZA to the active control, prednisolone acetate suspension 1% (PAS). For the efficacy of DEXTENZA in the adult subjects with ocular pain and inflammation following cataract surgery, all the three Phase 3 studies compared DEXTENZA with placebo (not PAS) in the double masked design. All studies had formal statistical hypothesis and testing. Moreover, PAS was approved in 1973, there were no clinical data found for either adult or pediatric studies. Therefore, the evidence of efficacy was inconclusive for DEXTENZA comparable to PAS for the treatment of ocular inflammation and pain following cataract surgery in pediatric subjects.

5.3 Conclusions and Recommendations

Only descriptive statistics were provided for the primary efficacy endpoints in the reviewed open-label pediatric Study CLN-Protocol-0050. There was no formal hypothesis and statistical testing

proposed for the comparison of DEXTENZA to the active control, prednisolone acetate suspension 1% (PAS). The efficacy of DEXTENZA in adult subjects was evaluated in the studies where DEXTENZA was compared with placebo (not PAS) in the double masked design. For PAS approved in 1973, there were no clinical data found for either adult or pediatric studies. Therefore, the data was limited, and the evidence of efficacy was inconclusive for DEXTENZA comparable to PAS for the treatment of ocular inflammation and pain following cataract surgery in pediatric subjects.

6 Appendix

6.1 Demographic and Baseline Characteristics

Table 14: Demographic Characteristics of Study CLN-Protocol-0050

Characteristic	Dextenza (N=37)	PAS (N=32)	Overall (N=69)
Gender, n (%)			
Male	25 (67.6)	18 (56.3)	43 (62.3)
Female	12 (32.4)	14 (43.8)	26 (37.7)
Age (years)			
N	37	32	69
Mean (SD)	1.2 (1.44)	1.4 (1.61)	1.3 (1.51)
Median	1.0	1.0	1.0
Min, Max	0, 4	0, 4	0, 4
Ethnicity, n (%)			
Hispanic or Latino	4 (10.8)	4 (12.5)	8 (11.6)
Not Hispanic or Latino	33 (89.2)	28 (87.5)	61 (88.4)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	1 (2.7)	0	1 (1.4)
Black or African American	1 (2.7)	2 (6.3)	3 (4.3)
Native Hawaiian or Other Pacific Islander	0	0	0
White	33 (89.2)	27 (84.4)	60 (87.0)
Other	2 (5.4)	1 (3.1)	3 (4.3)
Multiple	0	1 (3.1)	1 (1.4)
Unknown	0	1 (3.1)	1 (1.4)
Iris Color, n (%)			
Black	0	0	0
Blue	23 (62.2)	16 (50.0)	39 (56.5)
Brown	11 (29.7)	12 (37.5)	23 (33.3)
Green	1 (2.7)	2 (6.3)	3 (4.3)
Grey	1 (2.7)	0	1 (1.4)
Hazel	1 (2.7)	2 (6.3)	3 (4.3)
Other	0	0	0

Source: Clinical Study Report Section 11.2.1

Table 15: Baseline Ocular Characteristics (Safety Population) in Study CLN-Protocol-0050

Characteristic	Study Eye			Non-Study Eye		
	Dextenza (N=37)	PAS (N=32)	Overall (N=69)	Dextenza (N=37)	PAS (N=32)	Overall (N=69)
Anterior Chamber Cells, n (%)						
n [1]	33	31	64	33	31	64
Grade 0	33 (100)	31 (100)	64 (100)	33 (100)	30 (96.8)	63 (98.4)
Grade 0.5	0	0	0	0	1 (3.2)	1 (1.6)
Grade 1+	0	0	0	0	0	0
Grade 2+	0	0	0	0	0	0
Grade 3+	0	0	0	0	0	0
Grade 4+	0	0	0	0	0	0
Anterior Chamber Flare, n (%)						
n [1]	33	31	64	33	31	64
Grade 0	31 (93.9)	29 (93.5)	60 (93.8)	31 (93.9)	29 (93.5)	60 (93.8)
Grade 1+	2 (6.1)	2 (6.5)	4 (6.3)	2 (6.1)	2 (6.5)	4 (6.3)
Grade 2+	0	0	0	0	0	0
Grade 3+	0	0	0	0	0	0
Grade 4+	0	0	0	0	0	0
Intraocular Pressure (mmHg)						
n	28	25	53	27	25	52
Mean (SD)	12.3 (4.62)	12.8 (4.91)	12.6 (4.72)	13.0 (5.25)	12.8 (4.03)	12.9 (4.66)
Median	10.5	13.0	12.0	13.0	13.0	13.0
Min, Max	5, 21	4, 23	4, 23	6, 30	4, 20	4, 30

Characteristic	Dextenza (N=37)	PAS (N=32)	Overall (N=69)
FLACC Pain Score			
n [1]	37	32	69
Mean (SD)	0.2 (1.32)	0.4 (1.88)	0.3 (1.59)
Median	0.0	0.0	0.0
Min, Max	0, 8	0, 10	0, 10
FLACC Pain Score, n (%)			
n [1]	37	32	69
0	36 (97.3)	30 (93.8)	66 (95.7)
1 to 2	0	0	0
3 to 4	0	1 (3.1)	1 (1.4)
5 to 6	0	0	0
7 to 8	1 (2.7)	0	1 (1.4)
9 to 10	0	1 (3.1)	1 (1.4)

Source: Clinical Study Report Section 11.2.2

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